COMMENT

Human papillomavirus vaccines, complex regional pain syndrome, postural orthostatic tachycardia syndrome, and autonomic dysfunction – a review of the regulatory evidence from the European Medicines Agency

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Abstract

Recent concerns about a possible association between exposure of young women to human papillomavirus (HPV) vaccines and two "dysautonomic syndromes" (a collection of signs and symptoms thought to be caused by autoimmunity) — complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) — led the European Medicines Agency (EMA) to review existing evidence. The review was announced by the EMA on July 13, 2015, and was completed on November 4, 2015.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) carried out the review. The PRAC's review process was confidential. It concluded that there was no evidence of an association between the HPV vaccines and CRPS and POTS despite the existence of independently clustered reports or "signals".

Against the background of the public health importance of HPV vaccines and the secrecy surrounding the EMA's review process, this paper brings together relevant hitherto unseen and uncensored procedural review documents from both the manufacturers and the EMA to assess the process behind the EMA review and expose it to public view by making the documents available.

The PRAC review was carried out in close collaboration with the HPV vaccines' three manufacturers: GlaxoSmithKline Biologicals, Merck Sharp & Dohme Limited, and Sanofi Pasteur MSD. The documentation assembled raises several questions about the quality of the EMA review.

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Introduction

Since 2006, bivalent bHPV (Cervarix™), and quadrivalent qHPV (Gardasil™ and Silgard™) vaccines have been licensed for the prevention of cervical cancer and other diseases caused by HPV, such as genital warts and anal cancer. As of June 30, 2015, bHPV and qHPV are estimated to have sold 57 million and 190 million doses respectively (Table 1: C, p 106; E, p 17)[1]. The European Medicines Agency (EMA) approved the vaccines for use in the European Union. According to European law, the manufacturers are legally accountable for the quality, safety and efficacy of their HPV vaccines. The EMA, in turn, is accountable for the protection of public and animal health through the scientific evaluation and supervision of medicines that it approves. The culture of secrecy in the EMA has been an object of concern (1) and the European Ombudsman made similar observations about EMA regulations (2). This has led to an increase in EMA transparency starting in 2010, mainly related to the release of regulatory documents on application (3).

On May 26, 2016, a formal complaint (the first author of this paper is among the signatories) was made to the EMA regarding its conclusion in November 2015 that it could find no evidence of an association between the HPV vaccines and two "dysautonomic syndromes", collections of signs and symptoms thought to be caused by autoimmunity, which are triggered by external stimuli such as vaccination (4). The two dysautonomic syndromes referred to were complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS)[2]. The complaint listed a series of procedural criticisms of the EMA's HPV vaccines review (5).

This paper is a synthesis of the evidence presented to the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) by the HPV vaccines' three manufacturers or marketing-authorisation holders (MAHs): GlaxoSmithKline Biologicals, Merck Sharp & Dohme Ltd and Sanofi Pasteur MSD. The PRAC, which started work in July 2015, used this evidence to conclude that there was no association between the HPV vaccines and CRPS or POTS.

In this commentary, we bring together relevant hitherto unseen and uncensored documents from both the manufacturers and the EMA. Some documents were obtained

through an application under the Freedom of Information Act. Two documents were shared with us. We examine these documents in an attempt to assess the process behind the EMA review. Our assessment raises questions on the transparency and replicability of the PRAC's review.

No paper can summarise in a few thousand words the large quantities of European regulatory documents generated by the issue of HPV vaccines and autonomic dysfunction. For this reason, we have made the documents available to readers, cross-referencing each document in the text. The reader may refer to the documents and gain further insights into any aspect which we do not discuss in our review.

The PRAC consists of members from the European Union who are nominated by the European Commission and Parliament. Members serve three-year terms. Committee members are bound to secrecy. There is a stark reminder of this in the opening pages of the Committee's main document. (Table 1: G, p 2) (highlights added):

Confidentiality Reminder

As an EMA expert you are bound to life-long duty of confidentiality. The duty of confidentiality applies to all information of the kind covered by the obligation of professional secrecy. This includes, for example, the fact that there is a meeting, that you have been nominated to participate, the agenda of the meeting, the product or company concerned, the participants, any part of the discussions and outcome. All documentation (correspondence, reports, minutes, etc.) must be kept as confidential and stored in a secure place or destroyed. The duty of confidentiality stops only if information has been made public and only to the extent that has been released into the public domain. If you are not sure if certain information is in the public domain, then please seek guidance from the EMA.

Outside official communications, such as during an official meeting at the EMA, you should not communicate about any aspects covered by confidentiality with anyone except the EMA experts appointed for the meeting, the relevant EMA staff and PRAC/CHMP members. In particular, you should avoid any communication with persons associated with the concerned pharmaceutical company, including their staff, experts and advisors, or any other interested party (or competitors). Failure to do so may also affect your impartiality and modify your level of conflict of interest. You should inform the EMA if pharmaceutical companies or other interested parties are attempting to liaise with you seeking to provide or obtain information in connection with your activity of EMA expert.

The potential "signals"

The practice of monitoring the effects of vaccines or drugs after licensing is called pharmacovigilance. Pharmacovigilance relies on "signals", reported information on a possible causal relationship between an adverse event and a vaccine/drug (with the relationship previously being unknown or incompletely documented).

Starting in 2013, three clusters of signals of a possible link between HPV vaccines and CRPS and POTS were reported.

1) In 2013, Kinoshita et al from Japan reported 40 young women (aged 11 to 17 years) who developed dysautonomic symptoms after vaccination for HPV. Eighteen were diagnosed with CRPS and four with POTS. The authors noted that HPV vaccination possibly had an involvement in the genesis of CRPS and POTS since the average time to onset was 5.47 months ± 5 months post vaccination (Table 1: A, p 23) (6).

2) In 2015, Brinth et al from Denmark reported 53 young women (aged 12 to 39) who developed dysautonomic symptoms within two months after vaccination for HPV (7). The majority of the women (>50%) met the POTS diagnosis criteria. However, the authors noted: "POTS should probably be looked upon as a symptom secondary to another, yet unidentified condition rather than as a disease entity of its own." (Table 1: A, p 23). The authors' note presumably stems from the vast heterogeneity in symptomatology – headache (100%), orthostatic intolerance (96%), fatigue (96%), nausea (91%), and pain (70%) – reported by the women. A similar, smaller case series of six women was also reported from the US (Table 1: D, p 3).

3) In 2015, the World Health Organization (WHO) Uppsala Monitoring Centre reported a signal consisting of 21 young women (aged 11 to 26) with some overlap between CRPS and POTS symptomatology. They hypothesised that this was due to a common underlying autoimmune aetiology. For 18 of the 21 cases, the reported time to onset ranged from one day to two years post-vaccination with a median of 8-13 days. This led the WHO Uppsala Monitoring Centre to recommend further investigation, stating, "… the potential for a common pathology [sic]…warrants attention." (Table 1: A, pp 20-2).

As of August 3, 2015, the WHO Uppsala Monitoring Centre's database contained a total of 94 HPV vaccine-related reports for CRPS, of which 65 were described as "serious", and 147 HPV vaccine related reports for POTS, of which 117 were described as '"serious" (8)(Table 1: D, pp 1-2).

The EMA's safety referral procedure

On July 13, 2015, the EMA announced that a safety referral procedure (a procedure used to resolve concern issues over

Table 1: Documents used as a source of data and information

Serial	Document Title	Link	Source. content	Notes
A	*Chandler R E. HPV vaccine and gastrointestinal motility disorders, 2015. Signal - analysis of reports in the WHO Global ICSR. Database - Vigibase April 2015.*	http://ijme.in/pdf/a-signal-2015-print.PDF	FOI. Eight-page article in WHO's Signal restricted magazine on HPV vaccine and Gastrointestinal motility disorders. Response from Market Authorisation Holders	Dated April 2015.
B	*WC500189476 (Referral announcement)*	http://ijme.in/pdf/b-wc500189476-referral-announcement.pdf	EMA. Two-page letter announcing EMA start of the procedure	Dated July 13, 2015
C	*R - ema-responses-prac-crps-pots*	http://ijme.in/pdf/c-r-ema-responses-prac-crps-pots.pdf	FOI. MSD and Sanofi MSD response to EMA questions (188 pages). Excerpts are subsumed into "Briefing note to Experts (serial G)"	Dated July 2015.
D	*Report from WHO Uppsala Monitoring Centre regarding cases in VigiBase®*	http://ijme.in/pdf/d-finalised-report-for-danish-health-and-medicines-agency.pdf	Private source. Report sent to the Danish Health and Medicines Agency on August 26, 2015(25 pages)	Summer 2015
E	*R - Cervarix ema-responses-safetyart20crpsandpots*	http://ijme.in/pdf/e-r-cervarix-ema-responses-safetyart20crpsandpots.pdf	FOI. GSK response to EMA questions (91 pages). Excerpts are subsumed into "Briefing note to Experts" (serial G)	Undated
F	*R - HPV (Silgard, Gardasil) Co-Rapporteurs AR*	http://ijme.in/pdf/f-r-hpv-silgard-gardasil-co-rapporteurs-ar.pdf	FOI. PRAC Co-rapporteurs' report (103 pages)	Dated September 18, 2015
G	*Briefing note to the experts_ EMA_Oct 2015*	http://ijme.in/pdf/g-briefing-note-to-the-experts-ema-oct-2015-unredacted.pdf	Private source. Notes for SAG meeting held on 21 Oct 2016 (256 pages)	Dated October 13, 2015.
H	*R - HPV vaccines referral SAG vaccines final answers*	http://ijme.in/pdf/h-r-hpv-vaccines-referral-sag-vaccines-final-answers.pdf	FOI. Minutes and responses to PRAC from the SAG Vaccines meeting on HPV vaccines 21 October 2015.EMA reference: EMA/702401/2015	Dated November 4, 2015
I	*EMA response to Nordic Cochrane letter on HPV vaccines - maladministration*	http://ijme.in/pdf/i-ema-response-to-nordic-cochrane-letter-on-hpv-vaccines-maladministration.pdf	EMA. (17 Pages)	Dated July 1, 2016

***Key**: EMA = European Medicines Agency; FOI = Freedom of Information; PRAC = Pharmacovigilance Risk Assessment Committee; SAG = Stakeholders Advisory Group*

Table 2:
V501 (qHPV) studies contributing data to MAH review for PRAC, by EMA-held status.

Study ID	Clinical study report held by EMA	Included in manufacturers' review	Held by EMA and included in the review
005	Y	N	N
007	N	Y	N
011	N	Y	N
012	Y	Y	Y
013	Y	N	N
015	Y	Y	Y
016	Y	Y	Y
018	Y	Y	Y
019	Y	Y	Y
020	Y	Y	Y
024	N	Y	N
025	N	Y	N
029*	N	N	N
030*	N	N	N

**Studies 029 and 030 are listed but not held by EMA.*

vaccine or drug safety) on HPV vaccines would be held and overseen by its PRAC (Table 1: B, pp 1-2). The PRAC nominated from among its members "rapporteurs" and "co-rapporteurs" "who take the lead in the scientific assessment and who have the task of thoroughly assessing the data and drafting their recommendations which is then shared with all PRAC members." (Table 1: I, p 4).

Shortly after, the PRAC outlined five questions to be answered by the manufacturers (Table 1: C, p 4). The manufacturers' responses were augmented by the PRAC's review of the evidence and of data from public submissions and pharmacovigilance databases (such as EudraVigilance).

An assessment of the five questions formulated by the PRAC (and answered by the manufacturers) follows.

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.*

The manufacturers answered these two questions with reference to their database of clinical trials (Table 2 for the qHPV trials and Table 3 for the bHPV trials). They used very similar methods. They searched in their databases for cases that had been labelled by trial investigators and pharmacovigilance reporters as CRPS and POTS, or cases that had one or more features suggestive of either syndrome (Table 1: C, p 8; E, p 35). They then listed and described the cases with CRPS and POTS "preferred terms"[3]. The case numbers and the country of incidence were redacted from the manufacturers' reports.

The response to both questions gives a list of clinical trials. However, the criteria for inclusion in the analysis – and exclusion from analysis – were not clearly articulated. This poses a problem for any reproducibility of the results of the review, even given access to the trials' reports.

Table 3:
bHPV studies contributing data to the manufacturers' review

Study ID	Clinical study report held by EMA	Included in manufacturers' review	Held by EMA and included in the review
HPV-001	Y	Y	Y
HPV-004	Y	N	N
HPV-005	Y	N	N
HPV-007	Y	N	N
HPV-008	Y	Y	Y
HPV-009	Y	Y	Y
HPV-012	Y	N	N
HPV-013	Y	Y	Y
HPV-014	Y	N	N
HPV-015	Y	Y	Y
HPV-020	Y	Y	Y
HPV-021	Y	Y	Y
HPV-023	Y	N	N
HPV-026	N	Y	N
HPV-029	Y	Y	Y
HPV-030	Y	Y	Y
HPV-031	N	Y	N
HPV-032	N	Y	N
HPV-033	Y	Y	Y
HPV-035	N	Y	N
HPV-036	N	Y	N
HPV-038	N	Y	N
HPV-048	Y	N	N
HPV-049	Y	N	N
HPV-058	N	Y	N
HPV-069	N	Y	N
HPV-070	Y	N	N

For example, the MSD submission to the Committee reports that "The Market Authorisation Holder reviewed data from all clinical studies of the qHPV vaccine (V501 clinical programme) and 9vHPV [nine-valent] vaccine (V503 clinical programme) *which supported global filings* where subjects received the qHPV vaccine, or 9vHPV vaccine, or placebo" [emphasis added]. There is no exhaustive list of all trials and the wording suggests that only data from "useful trials" were included (ie only those used to apply for licensing). The list of trials submitted by MSD to the PRAC does not seem to correspond to the list of trials known to have been submitted to the EMA on its qHPV vaccine (Table 1: C, p 5; E, p 34).

Similarly, the reasoning given for the exclusion of data from multivalent (ie >4 HPV types) unregistered HPV vaccine trials is unclear. The explanation is: "… these investigational HPV vaccines differ from the qHPV vaccine" and "…they [the young women] had received marketed qHPV vaccine prior to enrolling." (Table 1: C, p 6).

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.*

As the question suggested, the manufacturers constructed incidence rates (for "comparison to those expected in the target population") for CRPS and POTS within their own data holdings, using the number of vaccine doses distributed as a denominator (Table 1: C, p 69, p 94; E, p 80). The comparisons are based on *estimates* of incidence rates. The manufacturers had difficulties in reconstructing both observed and expected rates. GlaxoSmithKline estimated POTS incidence to be between 15 and 140/100.000 in "best" vs. "worst case" scenarios. Because of uncertainty of doses administered in the case of bHPV, GlaxoSmithKline performed sensitivity analyses for the rate assumptions for POTS background incidence rates (Table 1: E, p 57). Sensitivity analyses are useful for assessing the impact of uncertainty on the conclusions. Such analyses are based on different scenarios with different assumptions (in this case incidence rates of POTS). By varying the incidence rates, the analysis can identify any change in conclusions.

After describing the possible CRPS and POTS cases known to them, the manufacturers pointed out systematic weaknesses in the data (unfulfilled case definitions, case underreporting, absence of denominators, and rudimentary descriptions). They then concluded that the information assessed was insufficient to provide evidence of a possible association between CRPS/POTS and exposure to 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.

The manufacturers answered this question by analysing available published studies (including large observational studies) and proposed pathophysiological mechanisms involved in the genesis of CRPS and POTS. The manufacturers' overall conclusion was that there was no evidence of a biological mechanism of association with HPV vaccines and CRPS and POTS. GlaxoSmithKline's conclusion, however, provides some minor explanations: "...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." (Table 1: E, p 86).

Question 5: *The MAHs should discuss the need for possible risk minimisation tools and provide proposals as appropriate.*

The manufacturers responded indicating that despite the lack of evidence, they would continue to survey case reports of CRPS and POTS and related symptomatology (Table 1: C, p 174; E, p 90).

The EMA PRAC's review: a synthesis of the manufacturers' answers to the PRAC's five questions

The co-rapporteurs' preliminary assessment report was shared with the stakeholder advisory group as a "briefing note" (Table 1: G). The co-rapporteurs were expected to "… take the lead in the scientific assessment" and were given "…the task of thoroughly assessing the data and draft their recommendations." The stakeholder advisory group then provided "the EMA's scientific PRACs with an expert view to complement the expertise of the regulatory network" (Table 1: H, p 6).

After the PRAC's consultation with the stakeholder advisory group, an updated assessment report was produced and circulated to all parties involved, including the manufacturers.

The PRAC then "…reached its scientific recommendation by consensus following plenary discussion." This recommendation was presented in the final PRAC assessment report, which summarised all the data assessed in support of the PRAC's conclusion (Table 1: I, p 5).

The recommendations were then forwarded to the EMA Committee for Medicinal Products for Human Use which held a review and a plenary discussion and then issued its conclusions. Finally, the European Commission issued its Commission Decision, approving the referral procedure (Table 1: I, p 5).

A 40-page Procedure Assessment Report was made available online (9)

The rapporteurs' contribution

As an EMA expert, the rapporteur is "…bound to *life-long duty of confidentiality*. The duty of confidentiality applies to all information of the kind covered by the obligation of professional secrecy…" [emphasis added] (Table 1: G, p 2).

The rapporteurs' confidential report or briefing note to the stakeholder advisory group in the HPV review, dated October 13, 2015 (Table 1: G), is in large parts, based on the manufacturers' reviews. For example, the rapporteurs' conclusions are similar to those of the manufacturers and recommend the "maintenance of the Market Authorisation" (ie status quo) (Table 1: G, pp 7-8, p 241).

However, there was a disagreement between the rapporteurs. "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." The rapporteur attributes the higher rates of reporting from Denmark and Japan to the "publicity around HPV vaccine safety" and concludes that there is a lack of clear "signal" for both CRPS and POTS (Table 1: G, p 247). There is, therefore, no need to change the benefit-risk ratios for the vaccines (Table 1: G, pp 7-8).

Representations by two Dutch physicians (Dr Luc Kiebooms and Dr Andre Devos) are also discussed - and dismissed by the PRAC. The physicians make a number of points on the effectiveness and safety profile of the HPV vaccines. They recommend a surveillance of harms to be carried out independently of the manufacturers (Table 1: G, pp 171-7).

The rapporteurs also reproduced a table of "CRPS reporting rates per million vaccinees" directly from the manufacturers' submissions (Table 1: G, p 48). Approximately half of the table information has been redacted in the PRAC's review prior to its release under the Freedom of Information rules (Table 1: C, p 69). The information from the tables is reproduced overleaf.

Discussion

The documents presented here are numerous and complex. Their data content comes from different sources. We cannot discuss the strengths and limitations of the documents' content in detail, but a few points stand out.

The limits of pharmacovigilance in relation to the EMA PRAC review

The limits and consequences of pharmacovigilance are well known. Pharmacovigilance includes the most dependable (the results of randomised clinical trials) as well as perhaps the least dependable measure of adverse events: spontaneous ad hoc reporting.

Clinical trials are designed and conducted to test specific hypotheses. Study design, choice of comparator (ie vaccine compared with placebo) and reporting are all key elements to evaluate a trial and its risk of bias.

The presence of comparators and the chance to compare vaccines with placebo by randomisation and blinding present unique opportunities to answer difficult questions about

Table 5
CRPS Reporting Rates per Million Vaccinees

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

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	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)

adverse events, such as the ones posed by the PRAC. Correct trial design ensures that any outcome differences observed between the arms are most likely due to the intervention (in this case HPV vaccines) alone.

However, the EMA review focuses largely on CRPS and POTS case reports. Unlike trial data, case reports lack controls. As a consequence, inferential statements cannot be made, though hypotheses may be generated.

Most case reports of CRPS and POTS were assembled in busy clinics and often lacked background detail, preventing comparison to a pre-specified definition. Moreover, reporting rates of CRPS and POTS were probably linked to an awareness of local vaccine issues, and may have originated in countries or treatment centres where CRPS and POTS for some reason caught attention.

However, despite some of the events reported being causes for concern, the PRAC did not consider the signals sufficiently robust, regardless of where they came from. Although some of the criticisms of the reports' data quality are well founded, if pharmacovigilance is able to produce only bad quality data, has no comparators, and as a consequence is unable to help in similar situations, why collect such data? Why do we continue with the practice of pharmacovigilance at all?

The limits of pharmacovigilance are also some of the same limits of modern epidemiology in its current state of development. These are: difficulty in generalising from a few cases to a population and vice versa (in this case from the handful of reported cases from certain states to a worldwide population of tens of millions); significance testing relying on huge datasets for rare outcomes; and the lack of integration between all types of evidence (in-vitro, animal and human). This means that no definitive assessment can be made on potential harms like CRPS and POTS.

The question of a potential harm in the HPV vaccine poses a difficult situation, because the vaccine is offered to – and is in some places compulsory for – healthy women.

The limits of the PRAC review

The PRAC based its judgements on aggregate data provided by the manufacturers. It did not check the manufacturers' results, carry out independent analyses, or access the raw data of the trial datasets presented in the manufacturers' responses. Furthermore, there are fundamental contradictions in the documentation, and no indication that the PRAC conducted independent re-analyses of the data provided by the manufacturers. It is likely that the PRAC did not assess a major part of the manufacturers' data. This is evident when one takes a closer look at the process:

First, the EMA stated in its initiatory referral announcement letter (dated July 13, 2015) that it would "…*not address the question of whether the benefits of HPV vaccines outweigh their risks*" (Table 1: B, p 1). So it is surprising that the EMA decided to answer this question anyway, in its final public assessment report (from November 11, 2015): the "…*benefits of HPV vaccines continue to outweigh their risks*." (See (9), p 39). In fact, this seemed to be a foregone conclusion.

Second, the criteria for including trials are unclear and appear contradictory. One of the rapporteurs commented on this fact (Table 1: G, p 29).

Third, the PRAC did not assess one-fourth of the trials that contributed data to the analysis of potential CRPS and POTS cases. For the qHPV vaccine, the combined denominator (the total number of women) from trials presented by Merck Sharp & Dohme is 44.793 (Table 1: C, p 7). Cross referencing the HPV vaccine trial numbers with the EMA trial holdings reveals that the EMA does not hold clinical study reports for the trials: V501-007, V501-011, V501-024, and V501-025 (see Table 2). The total denominator (number of women) of these trials is 4427. That is 12% of the manufacturers' dataset that the PRAC does not seem to have checked (4427/36796, 12%). A similar mismatch is present for trials of bHPV (Table 3).

Fourth, at least four trials listed in the EMA qHPV holdings (or

that are known to the EMA) (see Table 2) are not included in the manufacturers' list (Table 1: C, p 7).

Finally, the PRAC uncritically reproduced the incidence rates of CRPS and POTS constructed by the manufacturers (Table 1: C, p 69, p 94; E, p 80; G, p 48)

Implications

It may be that the mismatch between the trials EMA holds and the trials included by the MAHs in their submissions have perfectly reasonable explanations. However, regulators and manufacturers must realise that both lack of clarity and unwillingness to make full disclosure generate conspiracy theories. This damages the public's confidence and distorts its views on vaccines or drugs and the use of these products.

The dismissal of the arguments by the two Dutch physicians, the rapporteur confidentiality requirements, and the reluctance of the PRAC to disclose the identities of their compilers and conflicts of interest all generate a feeling of secrecy surrounding the review (Table 1: G, p 2, pp 171-7).

Hypothetically, the manufacturers could have come to the conclusion (after assessing all post-marketing data) that the risk was greater than the potential benefit. So why would the EMA conduct the review if it would not question whether the HPV vaccines' benefits outweigh their risks?

Emerging questions about the EMA's regulation of the HPV vaccine

The documents in Table 1 raise questions about the nature and quality of regulation by the EMA with respect to the HPV vaccine. It appears that the outcome of the EMA's review process was decided prior to its initiation. The EMA's PRAC seems to have reproduced the manufacturers' responses without undertaking an independent analysis of the evidence. This may generate a suspicion that the EMA's review process had prejudged its outcome. A public health intervention (such as the HPV vaccines), which are given to millions of healthy women, needs transparent assessment of its public health role. No public health intervention should be shrouded in so much secrecy that it gives rise to suspicion. The EMA should consider alternatives to its secrecy requirements and cultivate a more transparent process of review – one that asserts the public trust in its evaluation. The EMA has recently made great strides towards greater transparency with the release of millions of pages of trial reports and other documents. However nothing short of complete transparency will do if the trust of the public and health professionals is to be deservedly retained.

Disclosures

TJ was a recipient of a UK National Institute for Health Research grant for a Cochrane review of neuraminidase inhibitors for influenza. In addition, TJ receives royalties from his books published by Il Pensiero Scientifico Editore, Rome and Blackwells. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011-13, TJ acted as an expert witness in litigation related to the antiviral oseltamivir, in two litigation cases on potential vaccine-related damage and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013).In 2014 he was retained as a scientific adviser to a legal team acting on oseltamivir. TJ has a potential financial conflict of interest in the drug oseltamivir. In 2014-16, TJ was a member of three advisory boards for Boehringer Ingelheim. He is holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. Between 1994 and 2013, TJ was the coordinator of the Cochrane Vaccines Field. TJ is a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the issues discussed in this work and the consequent complaint to the European Ombudsman.

LJ has no conflicts of interest to declare. LJ is an active member of the Danish organisation Doctors Without Sponsors.

Notes

1 Further details of the information referred to in this paper are available in the regulatory documents cited in this paper listed in Table 1, assigned a recognition letter (A to I) and hyperlinked. Where necessary, the relevant pdf page number is cited.

2 **Definitions of CRPS and POTS used by the EMA PRAC:**
Clinical diagnostic criteria for Complex Regional Pain Syndrome
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 * 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 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 * 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.
Source: Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine JJ. Validation of proposed diagnostic criteria (the 'Budapest Criteria') for Complex Regional Pain Syndrome. *Pain.* 2010 Aug;150 (2):268-74. doi: 10.1016/j.pain.2010.04.030. Epub 2010 May 20.
Clinical diagnostic criteria for Postural Tachycardia Syndrome
1. A heart rate increase of ≥30 beats per minute (≥40 beats per minute for adolescents) or a heart rate of ≥120 beats per minute from supine to standing position within 10 minutes;
2. Absence of orthostatic hypotension (orthostatic hypotension is defined as 20/10 mmHg blood pressure drop within 3 minutes from supine to standing position);
3. Symptoms of orthostatic intolerance lasting ≥6 months;
4. Symptoms exacerbated by standing and improved with recumbence;
5. Absence of other overt causes of orthostatic symptoms or tachycardia.
Source: Grubb B P. Postural Tachycardia Syndrome. *Circulation*. 2008 May 27; 117(21): 2814–17.doi:10.1161/CIRCULATIONAHA.107.761643

3 A Preferred Term is a distinct descriptor (single medical concept) for a

symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic. MedDRA Introductory Guide Version 14.0 iii March 2011 (pdf page 15). http://www.who.int/medical_devices/innovation/MedDRAintroguide_version14_0_March2011.pdf

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