Vaccinovigilance

Identification and Management of

Potential Risks Associated with Vaccines

Symposium on Vaccines

FAGG – AFMPS - FAMHP

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famhp
federal agency for medicines and health products

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.be

Disclaimer

Although I am a member of the Federal Agency for Medicines and Health Products (FAMHP), my presentation might not reflect the view of PRAC, EMA or the FAMHP.

My presentation is a personal viewpoint and binds in no way the organisations mentioned before.

Content

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Introduction

Definition of Vaccine Pharmacovigilance

Vaccine Pharmacovigilance: science and activities related to the **detection**, **assessment**, **understanding** and **communication** of **adverse events** following immunisation and other vaccine- or immunisation-related issues, and to the prevention of untoward effects of the vaccine or immunisation (CIOMS/WHO Group on Vaccine Pharmacovigilance)

Introduction

Terminology

- **AEFI: a**dverse **e**vents **f**ollowing **i**mmunisation, without necessarily having a causal relationship with the usage of vaccine
- **Immunisation:** the process of making a person immune
- **Vaccination:** administration of a vaccine

Introduction

Prophylactic vaccines specific issues

- Usually administered to large groups of healthy individuals
- Some vaccines are mandatory
- Concomitant administration
- Single-dose vaccine (No challenge/dechallenge)
- **High vaccine uptake → incident cases of natural diseases**
- Long-term immunological effects

Introduction

Prophylactic vaccines specific issues

- **Complex biological product**
- **Complex immunological response**
- Changes and variability in the manufacturing process
- Genetic, demographic and other characteristics of the vaccinees
- Population awareness → spontaneous reporting of AEFI
- Epidemiological changes induced by the vaccines

Guidelines – GVP

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 December 2013
EMA/488220/2012

Guideline on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases

Draft finalised by the Agency in collaboration with Member States	21 February 2013
Draft agreed by ERMS FG	8 March 2013
Draft adopted by Executive Director	9 April 2013
Start of public consultation	12 April 2013
End of consultation (deadline for comments)	12 June 2013
Revised draft finalised by the Agency in collaboration with Member States	23 October 2013
Revised draft agreed by ERMS FG	11 November 2013
Revised draft adopted by Executive Director as final	9 December 2013
Date for coming into effect after finalisation	13 December 2013

This Module focusses on vaccine-specific aspects and unique challenges that should be borne in mind when designing and implementing pharmacovigilance activities for vaccines.

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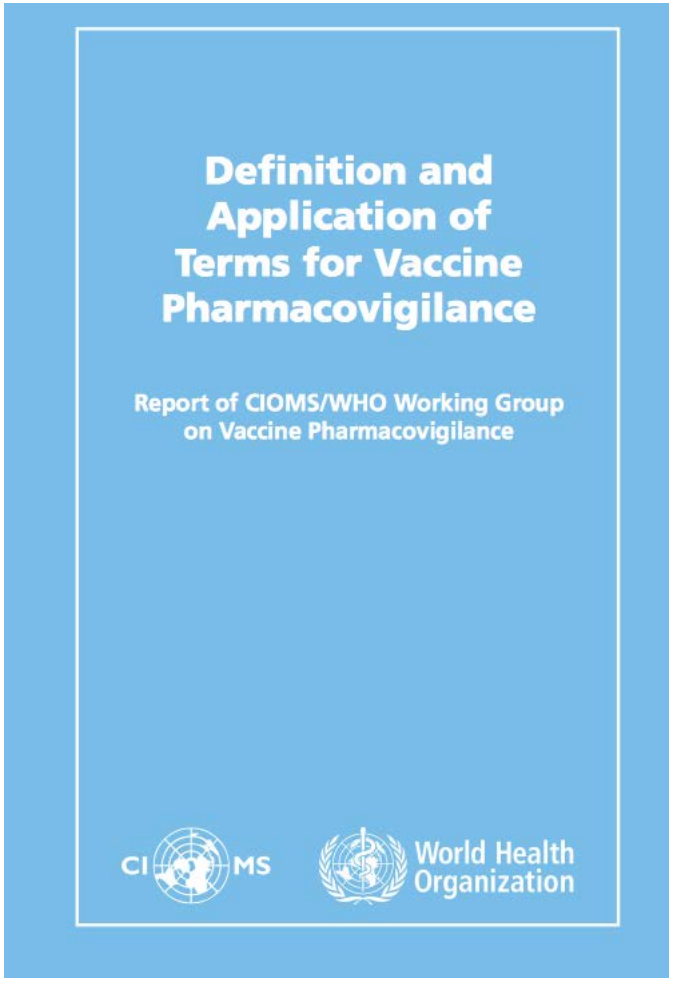
Guidelines – CIOMS / WHO Working Group



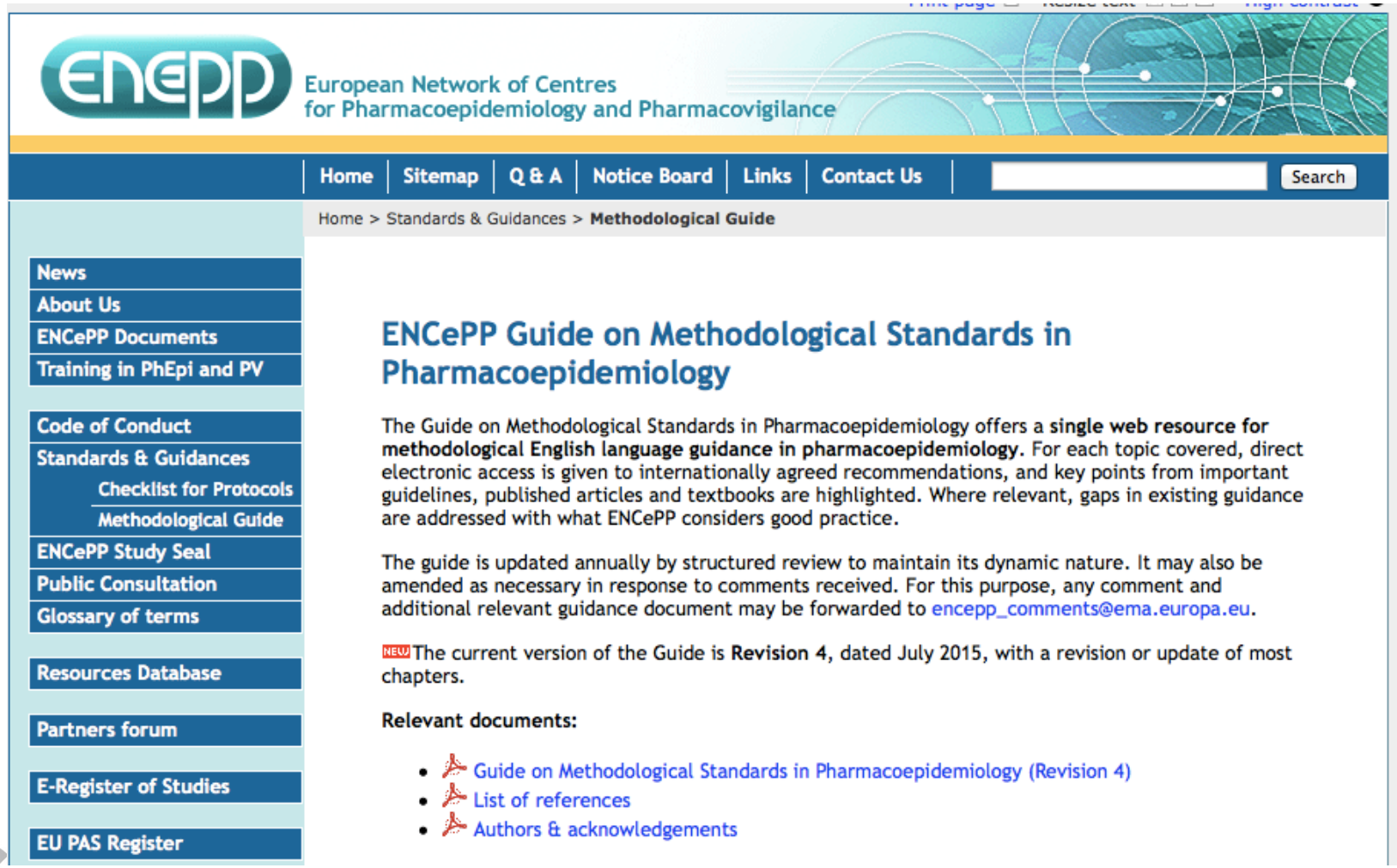
Report of CIOMS / WHO Working Group on Vaccine Pharmacovigilance, Geneva, CIOMS, 2012

The working group's report covers general terms and definitions for vaccine safety and discusses the application of such **harmonized tools in vaccine safety surveillance and studies**.

This report also highlights **case definitions for adverse events** typically reported for vaccines.

Guidelines -ENCePP

Guide on Methodological Standards in Pharmacoepidemiology



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ENCePP Guide on Methodological Standards in Pharmacoepidemiology

The Guide on Methodological Standards in Pharmacoepidemiology offers a **single web resource for methodological English language guidance in pharmacoepidemiology**. For each topic covered, direct electronic access is given to internationally agreed recommendations, and key points from important guidelines, published articles and textbooks are highlighted. Where relevant, gaps in existing guidance are addressed with what ENCePP considers good practice.

The guide is updated annually by structured review to maintain its dynamic nature. It may also be amended as necessary in response to comments received. For this purpose, any comment and additional relevant guidance document may be forwarded to encepp_comments@ema.europa.eu.

NEW The current version of the Guide is **Revision 4**, dated July 2015, with a revision or update of most chapters.

Relevant documents:

- Guide on Methodological Standards in Pharmacoepidemiology (Revision 4)
- List of references
- Authors & acknowledgements

Signals for vaccines

- **Data sources**
  - Spontaneous reporting, active surveillance, patients registries
  - Literature review
  - Observations, experiments, data mining …

Signals = New potentially (or new aspect of) causal association
Vaccine ←→ (set of) event(s)

Signals for vaccines

- **Management of signals**
  - Signal validation, confirmation
  - Prioritisation (B/R)
  - Signal assessment
    - Evidence on Epidemiologic and biologic plausibility
    - Post-authorisation safety & efficacy studies (PASS & PAES)
    - Mechanistic studies
  - Recommendation for action

Characterisation of the causal association:
confirmed, rejected, further investigation needed

Signals for vaccines

- **Standardised case definitions of adverse events** are a **key element for signal validation** and evaluation as they provide a common terminology and understanding of adverse events/reactions and thus allow comparability of data.
  - Definition published by the **Brighton Collaboration** should be used where available.
  - If a Brighton Collaboration definition is not available, the definition which is used should be carefully chosen based on scientific criteria and amenable.

  – Pandemrix: Narcolepsy
  – Rotavirus vaccines: Intussuseption
  – HPV vaccines … : CRPS and POTS ???

Signals for vaccines: single reports

- A single report of a serious adverse event should be processed as a signal **only if there is a possible causal association to the vaccine**.

- The validation of a report requires **adequate information** on:
  - the vaccination date
  - the clinical course of the event (time to onset, signs and symptoms, results of relevant laboratory and diagnostic tests, evolution, and treatment of the event)
  - medical and vaccination history
  - co-medication
  - details of the vaccine(s) administered (including brandname, batch number, route of administration and dose, site and route of administration)

Signals for vaccines: disproportionality

❑ Disproportionality analyses

– A statistical association does not imply **any kind of causal relationship** between the administration of the vaccine and the occurrence of the adverse events.

– Vaccines may require **special consideration** when applying such methods.

- Intrinsic differences between vaccines and other medicinal products
- The safety profile of a vaccine may differ substantially within the target population
- Caution required after a safety alert

Signals for vaccines: O/E

Observed / expected analyses: strengths

- Make best use of suspected adverse reaction reports.
- Observed vs. expected (O/E) analyses based on good-quality data can optimise the utility of passive surveillance data.
- Allow determination of the strength of a signal for prioritisation and further evaluation.
- Can help in **communication** of these data (particularly when serious, rare reported events are well within an expected range).

- **But**
  - Such analyses **cannot exclude risks or determine causality**

Signal for vaccines: O/E

Observed / expected analysis: limitations

- Observed
  - The ‘observed’ number of cases (underreporting)
  - The level of vaccine exposure
  - The levels of diagnostic certainty
- Expected
  - **The background incidence rates**

=> **sensitivity analyses** should be applied in statistical analyses around assumed levels of underreporting, numbers of ‘confirmed’ and ‘non-confirmed’ cases.

TV2 Denmark Documentary on HPV Vaccine Shows Lives of Young Women Ruined

Suspected side effects to the quadrivalent human papilloma vaccine

Louise Brinth[1, 2], Ann Cathrine Theibel[1, 2], Kirsten Pors[1] & Jesper Mehlsen[1, 2]

Methods: We present a description of suspected side effects to the Q-HPV vaccine in 53 patients referred to our Syncope Unit for tilt table test and evaluation of autonomic nervous system function.

Results: All patients had symptoms consistent with pronounced autonomic dysfunction including different degrees of orthostatic intolerance, severe non-migraine-like headache, excessive fatigue, cognitive dysfunction, gastrointestinal discomfort and widespread pain of a neuropathic character.

Conclusion: We found consistency in the reported symptoms as well as between our findings and those described by others. Our findings neither confirm nor dismiss a causal link to the Q-HPV vaccine, but they suggest that further research is urgently warranted to clarify the pathophysiology behind the symptoms experienced in these patients and to evaluate the possibility and the nature of any causal link and hopefully establish targeted treatment options.

DAN MED J 2015;62(4):A5064

29. May 2016 This Explains Last 2 Years' Illness

My now 16 yr old hasn't been to school for 3 semesters as she lay in her bed with intense daily migraines, eye pain, brain fog, etc. She was and hopefully still is a very smart girl, but her personality has changed as has her life, dramatically since getting this series of shots. I never put it together until last week when an article crossed my path. I new this was it. I've tried contacting her doctors and they all tell me I am wrong and there is no way. I doubt if they even spent time researching it. They just assume I am one of those mothers who complains about vacs, etc. etc.

12. March 2017 My Daughter has these symptoms

My daughter is 16 years old. She is suffering from 24/7 headaches, nausea, sore through and flu like symptoms. She had all 3 gardasil shots in 7th grade and was ill throughout year. They started becoming debilitating in her freshman year but she struggled through coming home often. This year she has barely made it to school and stays in a dark room the majority of the time. She has seen two neurologist, headache specials, ENT, Chiropractor, acupuncturist, eye doctors and no seems to see anything wrong with her. She is seeing a therapist as well. I've been doing a lot of research about the negative effects of Gardasil and feeling that is the possible cause to my daughters problems. I'm looking for someone who might be able to help with the proper detox with vaccine injuries. Can anyone help?

Side-effects stories affecting HPV vaccination numbers

Amongst the Nordic countries, Denmark holds the dubious record for having the fewest girls vaccinated a HPV

More information is needed if Denmark is to catch up with Nord
American Health Organization)

May 10th, 2017 11:07 am| by Stephen Gadd

More girls in Copenhagen refusing HPV vaccine

Reported side effects scaring young women away from cervical cancer protection

Girls are increasingly declining the HPV vaccine (photo: James Gathany)

April 27th, 2016 12:20 pm| by Ray W

Signals for vaccines: HPV, POTS & CRPS

- **Procedure: Article 20**
- Question: causal link between HPV vaccine and CRPS – POTS
- Population: young women vaccinated against HPV
- Methods
  - Questions:
    1. Review of data from clinical trials, post-marketing experience, literature
    2. Review of the cases in clinical trials
    3. Expected versus observed
    4. Strength of evidence for a causal association: review of epidemiological studies, pathophysiology, biological basis of a possible causal association
    5. Needs for risk minimisation tools
  - Response from the MAHs
  - Assessment by PRAC (pharmacovigilance risk assessment committee)
  - Conclusion and recommendation

O/E analysis for spontaneous data

	CRPS	POTS
N/dose distribution*	49/ 57,094 396 doses WW (0.086)	19 / 57,094 396 doses WW 0.033
Countries	Japan: 40/6,998 367 doses (0.57)	Japan: 8 /6,998 367 doses (0.11)
	UK : 8/8,669 742 doses (0.092)	UK: 10/8,669 742 doses (0.12)
	Republic of Korea: 1/2,278 546 doses (0.043)	US: 1/711 072 doses (0.14)
Risk periods	1 week, 1 year, 2 years	1 week, 1 month, 6 months and 1 year
Exposure	75% of doses distributed are administered (published exposure data was used in UK)	
Reported fraction	Proportion of CRPS/POTS cases reported among all those that occurred within the risk period (range: 1-100%)	
Case classification (safety scenario)	Best case: confirmed cases Mid-case: confirmed & unconfirmed cases Worst case: confirmed, unconfirmed & unlikely cases	
Data lock point	From launch on 17 May 2007 to 15 June 2015	
RESULTS	The observed incidence rate of CRPS or POTS following Cervarix vaccination **is not higher** than the expected rate for a range of plausible combinations of risk periods and reporting fraction, except for Japan in worst case safety scenario.	

***** Reporting rate (RR) per 100,000 doses distributed

CRPS: O/E analysis for spontaneous reports

Region/country	Assumed fraction of reporting	Safety scenario	Risk period	Results
Worldwide	2% 15% 23%	Best case Mid- case Worst case	1 week	Observed ≤ Expected
			2 years	Observed < Expected
UK	10% 36% 42%	Best case Mid- case Worst case	1 week	Observed ≤ Expected
			2 years	Observed < Expected
Republic of Korea	10%	Mid- case*	1 week	Observed ≤ Expected
			2 years	Observed < Expected
Japan	12% 71%	Best case Mid- case	1 week 2 years	Observed ≤ Expected
		Worst case	1 week	Observed > Expected**
			2 years	Observed < Expected

Signal for vaccines: HPV, POTS & CRPS

Limitations for the assessment

- Case definition → database queries
- Overlap of symptoms with other syndromes: SCF
- Incomplete medical histories: timing of events, diagnostic confirmation, absence of other causes, …
- Underreporting of cases (O/E)
- Limited epidemiological evidence
- Mechanistic process difficult to identify

Conclusion (EMA)

Review concludes evidence does not support that HPV vaccines cause CRPS or POTS

Reports of CRPS and POTS after HPV vaccination are consistent with what would be expected in this age group

5 November 2015
EMA/714950/2015

Signals for vaccines

- **Epidemiological studies**
  - Epidemiological studies **cannot establish causality** as the circumstances under which they are conducted often are observational in nature and therefore liable to confounding and bias (selection and information)
- **Mechanistic studies**

Conclusions

- Vaccination is one of the most effective and widely used public health intervention, whose benefits for individuals and the community have been abundantly demonstrated.
- Importance of transparency and communication to the outside world on the challenges, the signal management, the risk assessment, the impact of the risk minimisation … in the context of the benefits.
- "No vaccine is without risks but everything is at risk" → Need to educate the media
- Misinterpretation of adverse health outcomes that are only temporally related to vaccination will not only threaten the success of vaccine programmes, but also potentially hinder the development of newer vaccines.

Recommendations

- Development and availability of database that can provide locally relevant background rates of disease incidence are important to aid assessment of vaccine safety concerns
- Importance of quality database and data linkage
- Improve reporting (passive/active surveillance) and acurate exposure data
- Importance of case definitions for adverse events typically reported for vaccines (CIOMS)
- Epi studies should attempt to deal with awareness bias in sensitivity analyses
- Importance of mechanistic studies when association is detected, especially between the (adjuvanted) vaccine and unexpected AE for which the autoimmune aspect is unknown/challenged

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