An introduction to Vaccine Post-marketing Safety Surveillance

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01. Introduction to vaccine safety and adverse events
More than a century of vaccine experience

- Diphtheria antitoxin discovered
- Measles (live)
- Mumps
- Measles (live attenuated virus)
- Rubella
- Measles, mumps, rubella (MMR)
- Pneumococcal (14-valent polysaccharide)
- Human papillomavirus (Gardasil 9)
- Zoster (live) (PR5i)


- Measles, mumps, rubella, varicella
- *Haemophilus influenzae* type b/hepatitis B
- *Haemophilus influenzae* type b (liquid)
- Hepatitis A (inactivated)
- Varicella (chickenpox) virus
- *Haemophilus influenzae* type b (conjugated)
- Hepatitis B (recombinant)
- Pneumococcal (23-valent polysaccharide)
- Hepatitis B (plasma derived)
- Measles, mumps, rubella virus vaccine live (new rubella strain: RA 27/3)
Many important diseases are now largely forgotten in the US (and many other countries) due to vaccines.

![Image showing percentage decrease in disease rates due to vaccines](http://www.forbes.com/sites/matthewharper/2013/02/19/a-graphic-that-drives-home-how-vaccines-have-changed-our-world/)
Vaccine safety is critical to successful, sustainable vaccination programs

General public has **low tolerance to adverse events** as vaccines are usually given to healthy persons.

**Expectations to safety standard is higher** with vaccines compared to medicines for healthy people.

National regulatory authorities (NRAs) are responsible for the quality, safety and effectiveness of each vaccine licensed in their country.

Before being introduced, vaccines are assessed in clinical trials.

Once introduced, vaccines are thoroughly and continuously reviewed.

NRAs monitor and investigate adverse events following immunisation (AEFIs) to ensure safety for the population.

Adverse event following immunization (AEFI)

• An adverse event following immunization is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.
  
  • If not rapidly and effectively dealt with, can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence.

• Vaccine-associated adverse events may affect healthy individuals and should be promptly identified to allow additional research and appropriate action to take place.

Fig 1: Generic AEFI reporting flow chart ²


Association does not mean causation

Assess all case reports looking for features that may suggest a causal relationship between the use of the vaccine and the adverse event including:

- Dose-response Curve
- Biologic Plausibility
- Coherence
- Experimental Evidence
- Confounding Factors
- Strength
- Consistency
- Specificity
- Temporality
- Biologic Plausibility
- Coherence
- Experimental Evidence
- Confounding Factors
- Strength
- Consistency
- Specificity
- Temporality
Causality and risk-benefit assessments.

**CAUSALITY ASSESSMENT**
- A systematic review of data about an AEFI case, determining the **causal association** between the event and the vaccine
- Helps determine if an AEFI is attributable to the **vaccine or vaccine programme**, and what steps are needed to address the event
- Looks at **consistency**, **strength of association**, **specificity**, **temporal relation**, and **biological plausibility**

**RISK-BENEFIT ASSESSMENT**
- Addresses the **population at risk** (not the individual)
- Takes into account **contextual issues**
- **Economics**, availability of **alternative vaccines**, **sociopolitical** and **cultural factors**
- Prompted by a newly identified risk, but remains **holistic**
- Runs in parallel to active **enquiry**, **cooperation** and **exchange of info**
- Balances the need for urgent **action against** the need for **further investigation**

Vaccine safety systems are critical to maintain confidence in vaccines and vaccination programs

**History of vaccine safety concerns – US**¹

- 1955: Cutter incident and polio vaccines
- 1955-1963: Simian Virus 40 (SV40)
- 1976: Swine flu vaccine and Guillain-Barre Syndrome
- 1998: Hepatitis B and multiple sclerosis
- 1998-99: Rotavirus and intussusception
- 2005-2008: Guillain-Barre Syndrome and Meningococcal vaccine
- 2007: Hib vaccine recall
- 2009-2010: H1N1 influenza vaccine and narcolepsy
- 2010: Porcine circovirus in rotavirus vaccines

02. Vaccine safety monitoring institutions and stakeholders
Components of a 21\textsuperscript{st} century global vaccine safety monitoring, investigation and response system\textsuperscript{3}
Supranational, regional and some national institutions help strengthen, inform or guide national vaccine safety decisions

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<tr>
<th>Supranational</th>
<th>Regional</th>
<th>National</th>
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</thead>
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<tr>
<td>WHO Global Advisory Committee on Vaccine Safety (GACVS)</td>
<td>European Center for Disease Control</td>
<td>U.S. Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>• Respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance</td>
<td>• Conducts pharmacovigilence on behalf of NRAs</td>
<td>U.S. Food and Drug Administration</td>
</tr>
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<td>WHO Global Vaccine Safety Initiative</td>
<td>• Post-licensure surveillance</td>
<td>Australian Therapeutic Goods Administration</td>
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<td>• Establish guidance and indicators to ensure minimal capacity to ensure vaccine safety at national level.</td>
<td>• Technical support</td>
<td>Health Canada</td>
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<td>WHO Prequalification of Vaccines</td>
<td>European Medicines Agency</td>
<td>U.K. Medicines and Healthcare Products Regulatory Agency (MHRA)</td>
</tr>
<tr>
<td>• Prequalification for UN supply of vaccines</td>
<td>• Regulation</td>
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<tr>
<td>• Conduct quality assurance tests on individual vaccine batches, rigorously inspects manufacturing sites, and evaluates manufacturing countries’ NRAs.</td>
<td>• Pre/post licensure surveillance</td>
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The Global Advisory Committee on Vaccine Safety (GACVS) is the main global advisory body for vaccine safety advice and response.

GACVS provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short or long term national immunization programs. This includes providing advice on urgent matters as needed.

Rigorously reviews latest knowledge concerning any aspect of vaccine safety of global or regional interest, in close collaboration with all parties involved, including experts from national governments, academia, and industry;

Determines causal relationships between vaccines and/or their components and adverse events attributed to them;

Provides scientific recommendations which are intended to assist WHO, WHO's Strategic Advisory Group of Experts (SAGE) for vaccines and immunization, national governments and international orgs in formulating policies regarding vaccine safety issues.

Members (n=14) are acknowledged experts from around the world in diverse fields. Member have responsibility to provide WHO with impartial, high quality, scientific advice and recommendations on matters brought to the Committee.

03. Post marketed vaccine safety monitoring
A vaccine safety system is comprised of different types of surveillance across the lifecycle of a vaccine.

**Pre-licensure**
- Assesses safety, immunogenicity and efficacy
- Sensitivity of detection of uncommon or rare adverse events or those with delayed onset is low.

**Post-licensure**
- Identifies and evaluates rare events

**Passive Surveillance**
- Voluntary reporting by health care providers in daily practice

**Active Surveillance**
- Additional systematic surveillance by health authorities

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Different surveillance systems provide different types of information

**Vaccine Post-Licensure / Marketing Surveillance**

**Passive or Voluntary Reporting**
- Adverse events reported by health care providers, vaccinees, and others
  - Direct reporting to manufacturer
  - National surveillance systems
  - Multinational databases
- Identifies new or rare adverse events and changes in rates of previously reported adverse events
- Limitations: variability, reporter bias, potential underreporting
- Adverse event causality cannot be determined due to limited nature of data reported

**Active or Systematic Procedure**
- Manufacturer post marketing trials
- Large linked databases (e.g., US Vaccine Safety Datalink)
- Actively seeks and identifies clinically significant events that occur within a defined period and/or population
- Can assess whether a specific adverse event is significantly associated with vaccination

Vaccine PharmacoVigilance

• Vaccine PharmacoVigilance (PV), also known as Vaccine Safety, is:
  – Science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine or immunization-related issues\(^1\)

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Importance of Post-Market Safety (PMS) Surveillance in Global Health

- Despite very large clinical programs, much remains unknown about risks/benefits at time of introduction, especially in real-world settings
  - Society has very high expectations regarding safety; failure to address concerns may affect confidence in vaccine
- PMS safety concerns are in addition to those inherent in the drug/vaccine
  - Cold chain, proper administration, etc.
- Ongoing monitoring provides
  - Safety assessment
  - Rapid response to public, government, academia
  - Capability to maintain overall public confidence in all vaccines

Bill & Melinda Gates Foundation. Strengthening post-market surveillance in low and middle income countries (2014)
An Ideal Post-Licensure Safety Surveillance System

• Rapidly identifies safety issues that can be promptly and accurately assessed in order to facilitate public health decision making and optimize vaccine use

• Requires datasets that are
  • Representative of vaccinated population
  • Large (to detect rare events)
  • Reliable, accurate
  • Available in timely manner
  • Efficiently collected for analysis
Active Post-Licensure Safety Surveillance

- Post licensure clinical trial and Phase 4 studies (up to 100,000 participants)
  - To assess the effects of changes in vaccine formulation, vaccine strain, age at vaccination, number and timing of vaccine doses, simultaneous administration and interchangeability of vaccines from different manufacturers on vaccine safety and immunogenicity.
  - To improve the ability to detect adverse events that are not detected during pre-licensure trials, some recently licensed vaccines in developed countries have undergone formal phase 4 surveillance studies.
- Large linked databases, typically observational studies to:
  - Identify rare reactions
  - Monitor increases in known reactions
  - Identify risk factors for reactions
  - Monitor effectiveness in real-world conditions
  - Assess duration of protection and need for a booster
- PASS (Post-Approval Safety Study) more common in vaccines than small molecules
- Use of registries (e.g. vaccine safety in pregnancy)

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Role of PharmacoVigilance in Risk Management

• Once a product is marketed there is a large increase in the number of patients exposed to the product, including those with co-morbid conditions and those taking concomitant medications.

• Post-marketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product’s risk profile and for making informed decisions on risk minimization.

• PharmacoVigilance’s goal is to identify and evaluate safety signals in reports suggesting an excess, compared to what would be expected, of adverse events associated with a product’s use.

8 Understanding FDA Drug and Biologic Adverse Event Regulations.
Relatively Robust PharmacoVigilance system (US)

- Passive reporting system (spontaneous reports, e.g. VAERS)
  - +/−
- Mini-Sentinel Initiative (Mixed billing and EMR data)
  - +/−
- Vaccine safety datalink (Epidemiology assessment by chart review, often case-control)
  - +/−

- Safety signal detection (detects rare events)
- Enhanced safety signal detection (provides additional signal info)
- Formal safety signal assessment, e.g. PASS
04. Examples of signal detection and assessment
In Australia, the 2010 Southern Hemisphere a trivalent inactivated influenza vaccine (TIV) was associated with an increased risk of febrile seizures (rate ~1/100 doses).

ACIP recommended not using this TIV vaccine for children aged <9 years in the US.
US Monitoring for Febrile Seizures for the 2010-2011 Influenza Vaccine

- **VAERS**
  - Medical officer review of all possible seizure reports in children <5 years old who received influenza vaccine
  - Data mining in the VAERS database (to identify statistically disproportionate increased reporting)
- **VSD monitored seizures using Rapid Cycle Analysis**

Courtesy: F. DeStefano.
VAERS: Findings

• Data mining detected an increase in febrile seizure reports after one 2010-2011 influenza vaccine in children ages 6-23 months
• Clinical presentation was consistent with typical febrile seizures; all patients recovered

Courtesy: F. DeStefano.
VSD: Findings

- Detected signal for increased risk of febrile seizures on days 0-1 postvaccination among children ages 6-59 months who received first dose of TIV
- Most had received other vaccines, most commonly 13-valent pneumococcal conjugate vaccine (PCV13)

Courtesy: F. DeStefano.
VSD Attributable Risk Estimates for Febrile Seizures Following First-Dose TIV, 2010-11†


*Vaccines may have been received concomitantly with non-TIV, non-PCV13 vaccines.

Courtesy: F. DeStefano.
CDC Web Posting on Febrile Seizures Following TIV and PCV13†

†http://www.cdc.gov/vaccinesafety/Concerns/FebrileSeizures–archived.html

Courtesy: F. DeStefano.
Case Study:
European Medicines Agency review of HPV vaccines (Article 20)
And Post-Marketing Safety Surveillance
Global experience with Gardasil vaccine

- ~256 million doses distributed worldwide since 2006\textsuperscript{11}

- As of May 2017 Gardasil has been registered and approved in 134 countries

- Evidence from multiple countries demonstrates real-world impact of Gardasil vaccination on incidence of certain HPV-related diseases\textsuperscript{12–15}

- Continued monitoring by global regulatory agencies supports the safety profile of Gardasil vaccine\textsuperscript{16–19}

Please see slide notes for corresponding references.
HPV Vaccines under the 2015/16 Article 20 Procedure in Europe

- European Medicines Agency (EMA) investigates potential side effects of medicinal products for human use through the Pharmacovigilance Risk Assessment Committee (PRAC) under the Article 20 of Regulation (EC) No 726/2004.
- A review of all the HPV vaccines was initiated on 9 July 2015 by the European Commission (EC) at the request of the member state Denmark on reports of complex regional pain syndrome (CRPS, a chronic pain condition affecting the limbs) and postural orthostatic tachycardia syndrome (POTS, a condition where the heart rate increases abnormally after sitting or standing up, causing symptoms such as dizziness and fainting, as well as headache, chest pain and weakness).
- HPV vaccines are available in the European Union under the names Gardasil/Silgard, Gardasil 9, and Cervarix.
- It was estimated that at the time of the Article 20 review more than 63 million girls and women worldwide had been vaccinated with Gardasil/Silgard and more than 19 million with Cervarix.
Sensational media contributed to increase in reports of adverse events

- The Article 20 initiated by Denmark was due to reports on POTS, predominantly originating from that country, mainly from one treatment center, also encompassing CRPS a syndrome which primarily was reported in Japan.

- A reported suspected adverse reaction does not necessarily mean that there is a relationship between the vaccine and the symptoms experienced as adverse reactions to the vaccine

- There was an increase of SAE reports after a TV show aired in 2015
Identification of Potential Cases in The Databases* and Medical Evaluation

**STEP 1: RESEARCH THE DATABASES***

1. Pre-define groups of symptoms suggestive of the disease (based on accepted diagnosis criteria and agreement with the EMA)
2. Run queries to identify subjects who were reported to have the disease or who displayed any of the pre-defined groups of symptoms

**STEP 2: MEDICAL REVIEW**

Conduct medical review of all the information available in the database for cases suggestive of the disease to assess whether or not diagnosis criteria are met

*Including the clinical and post-marketing databases of Gardasil™ and Gardasil™ 9
Summary of Findings: Clinical Studies

- From our database of 60,594 subjects with 197,983 person-years follow-up we found:
  - Extremely low incidence of cases suggestive of CRPS and POTS
    - 3 cases suggestive of CRPS (1 each of the Gardasil 9, Gardasil, and placebo groups)
    - 2 cases suggestive of POTS (both in the Gardasil 9 vaccine group)
  - Incidence similar between the Gardasil 9, Gardasil, and placebo groups

- Medical review of the cases (using diagnosis criteria based on the published literature) indicated
  - Insufficient evidence to meet the diagnosis criteria for the 3 cases of CRPS and for 1 case of POTS
  - Diagnosis criteria met for 1 case of POTS

- Overall, this assessment does not suggest an association between HPV vaccination and CRPS or POTS
October 2015: Scientific Advisory Group conclusions

Scientific Advisory Group (SAG) conclusions - Oct 2015

“In conclusion, as far as feasibility of further studies is concerned, there are some designs which perhaps the PRAC could consider (e.g. CPRD study or similar retrospective designs), being aware of the risk of bias; however, in light of the lack of confirmed association so far, the question remains whether these are warranted at this stage.”

November 2015: PRAC conclusions

**Pharmacovigilance risk assessment committee recommendation (PRAC) – Nov 2015**

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.

The European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) has completed a detailed scientific review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women given human papillomavirus (HPV) vaccines. These vaccines are given to protect them from cervical cancer and other HPV-related cancers and pre-cancerous conditions. This review concluded that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil-9) and development of CRPS or POTS. Therefore there is no reason to change the way the vaccines are used or amend the current product information.

January 2016: Article 20 review process conclusions¹

HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS
Reports after HPV vaccination consistent with what would be expected in this age group

Reviewed newly licensed 4vHPV vaccine safety

Identified no safety profile concerns

Reviewed postmarketing surveillance data from 4 demonstration studies from developing countries and manufacturer’s studies

Found the safety profile of HPV vaccines to be reassuring

Reviewed data related to large-scale use of 4vHPV vaccine and postmarketing surveillance, including 3 publications on safety from independent investigators

Safety profile of 4vHPV vaccine was similar to data from prelicensure trials; found no sufficient cause to change previous advice on HPV vaccine safety

Reviewed evidence related to 4vHPV vaccine and MS and concerns about HPV vaccines and CRPS

Found no increased risk of MS with 4vHPV vaccine and no evidence to suggest causal link between HPV vaccines and CRPS

Reviewed 2 studies claiming association between aluminium in vaccines and autism spectrum disorders

Found serious flaws in both studies that limited their value even for hypothesis generation

WHO: Global Advisory Committee on Vaccine Safety (GACVS)

Globally monitors safety of all new vaccines, including 4vHPV vaccine

To date has not found any safety issue that would alter its recommendations for use of HPV vaccines

2007

Reviewed evidence related to large-scale use of 4vHPV vaccine and postmarketing surveillance, including 3 publications on safety from independent investigators

Safety profile of 4vHPV vaccine was similar to data from prelicensure trials; found no sufficient cause to change previous advice on HPV vaccine safety

2008

Reviewed 2 studies claiming association between aluminium in vaccines and autism spectrum disorders

Found serious flaws in both studies that limited their value even for hypothesis generation

2009

Reviewed evidence related to 4vHPV vaccine and MS and concerns about HPV vaccines and CRPS

Found no increased risk of MS with 4vHPV vaccine and no evidence to suggest causal link between HPV vaccines and CRPS

2012

Reviewed postmarketing surveillance data from 4 demonstration studies from developing countries and manufacturer’s studies

Found the safety profile of HPV vaccines to be reassuring

2013

Reviewed data related to large-scale use of 4vHPV vaccine and postmarketing surveillance, including 3 publications on safety from independent investigators

Safety profile of 4vHPV vaccine was similar to data from prelicensure trials; found no sufficient cause to change previous advice on HPV vaccine safety

2014

Reviewed newly licensed 4vHPV vaccine safety

Identified no safety profile concerns

2015

Identified no safety issue that would alter any current recommendations for use of 4vHPV vaccine

*Studies focused on syncope, hypersensitivity, anaphylaxis, and central demyelinating diseases. CRPS=complex regional pain syndrome; MS=multiple sclerosis; WHO=World Health Organization. Please see corresponding slide notes for references.
05. Post-Licensure safety assessment
Extensive Global Postlicensure Surveillance for qHPV Vaccine

- >16 postlicensure studies, including on-going studies, conducted in ~20 countries worldwide to assess long-term safety.
- Also assessed:
  - Long-term effectiveness
  - Long-term immunogenicity
  - Overall reduction in HPV-related disease burden
  - Ability of vaccination to complement cervical cancer screening programs
- One of the most comprehensive vaccine monitoring programs to date.

# Global Postlicensure Safety Surveillance of the qHPV Vaccine

<table>
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<tr>
<td>GARDASIL™ monitoring</td>
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Safet of Gardasil

PHASE III CLINICAL TRIALS

MORE THAN 29,000 Males and females aged 9-45

>15 POST-LICENSE STUDIES OVER 10 YEARS

MORE THAN 1 million Pre-adolescents, adolescents and adults from various countries

(Today, more than 2.4 million pre-adolescents, adolescents and adults.)

Conclusions: These results...confirm that the Gardasil has a FAVORABLE SAFETY PROFILE
GACVS considers HPV vaccines to be extremely safe.”

Conclusions

• Vaccines are among the safest and most effective public health interventions, yet on very rare occasions, they may cause severe adverse events.
• It is important to establish a reliable post-marketing safety surveillance system to monitor vaccine safety in order to detect and assess any possible signal and take action if necessary.
• Vaccine safety issues may be of interest locally, regionally, and sometimes globally.
• Rumors or news about vaccines can spread quickly and influence the perception of the safety of a vaccine at home: access to safety vaccine data will help control misinformation and public’s misperception.
• Spontaneous reporting is the cornerstone of most post-licensure safety monitoring systems because of its relative ease of implementation and ability to capture unexpected events.
Thank YOU