# About OMICS Group

OMICS Group is an amalgamation of Open Access Publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

# OMICS International Conferences

OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

# Vaccine Vigilance- Towards strengthening Pharmacovigilance

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Ex- Sanofi Pasteur and Serum Institute of India

# Introduction

- Immunization- the most cost-effective and widely used public health intervention
- A large number of vaccines are available
- Incidence of vaccine preventable diseases ↓ by vaccination; AEs due to vaccine and others coincidental become increasingly frequent and prominent*

*(CHEN R.T. et al, VACCINE, 12; 542-550, 1994)

# How Vaccines Differ from Drugs?

- Drugs are administered for an illness or condition while Vaccines are for prevention of illness. Intervention Vs Prevention!
- Adverse events to Vaccines indicate Immune Response and drug AEs are undesirable effects ( organ toxicity).
- This affects entire analysis, interpretation and implications of vigilance data.

(Cobert's Manual of Drug Safety& PV,2012)

# How Vaccines Differ from Drugs?

## Contd..

- Vaccines are given in large mass campaigns, subject less likely to have access to the provider & h/o illness, health condition may not be known.
- A drug AE results in HCP, being informed to follow up and treat.
- Little information maybe available on how many doses have been administered for a vaccine, to whom , with what results?
- ( H. Boelle, Med Sci, 2007,23(4),391-8)

# How Vaccines Differ from Drugs?

## Contd...

- No detailed safety information on Vaccines prior to licensure?
- Clinical trials are done on relatively small number compared to wide usage in millions post-licensure.
- Subjects at extremes of age are excluded.
- New vaccine does  not have data on special groups – pregnant, HIV +, cancer patients and elderly.

# GACVS - Europe

- GACVS ( Global Advisory Committee on Vaccine safety was established by WHO to address vaccine safety in Europe.
- Stressed on prompt data transmission by member states, assurance of data quality,

  & timely signal detection and action.
- It also stressed on safety of preservatives and non antigenic ingredients in vaccine manufacture / formulation.

# Role of Adjuvants

- Adjuvants, stabilisers, residuals like formaldehyde, viral growth media, vectors.
- Euvax project / VENICE (Vaccine European New Integrated Collaboration effort)
- Uppsala monitoring centre are programs used to strengthen all aspects of Immunization and vaccines worldwide.
- It is imperative that effective Vaccino-vigilance systems are maintained effectively.
- ( Bull World Health Organ, 2000,78(9):116)

# European Union AESIs

- Adverse events of special interest to Vaccines have been classified as they maybe linked with potentially serious AEs.
- Neuritis, Convulsions, Syncope, Vasculitis, Encephalitis, Thrombo-cytopenia, Bells Palsy, Gulliane -Barre syndrome are reportable events.

# Vaccine Related AES: Caveats

- Historically limited by gaps in knowledge on vaccine safety (Stratton K.R. et al, VACCINE 1160, 3rd edition, 1999).
- Inadequate scientific evidence to establish a causal link with vaccine
- Biological mechanisms unclear
- Insufficient or inconsistent information from case reports
- Inadequate size or length of follow-up of many population based epidemiological studies
- Limitations of existing surveillance systems to prove causation .
- Limitations in the health staff to record AEs

# Vaccine Related ADRS: Caveats

- Lack of expertise in pharmacoepidemiology and rare disease epidemiology with its special set of methodological challenges (FINE P.E.M., et al, *Am. J. Epidemiol.*)
- Interest and resource allocation for vaccine safety research- severely handicapped by narrow, negative terms of AE research; especially when competing against positive benefits and efficacy of vaccine
- Vaccine safety cannot be studied directly but can only be inferred by the absence of specific ADRs when appropriate surveillance and risk management systems are used

# Vaccine Pharmacovigilance: A Balancing Act

- This approach requires a systematic accumulation of negative findings which may be more difficult to prove than positive findings
- With the advent of reporting systems like VAERS and AEFI (WHO) it is important for all national programs to implement AE surveillance for immunization
- Recommendations for use of vaccines represent a dynamic balancing of risks and benefits in which vaccine safety monitoring is essential
- Further, research in vaccine safety can help distinguish true vaccine reactions from coincidental events and estimate their attributable risk as well as identify risk factors (MMWR 46 rr-3, 1997).

# The Importance of Vaccine Safety

- A higher standard of safety required than other pharmaceutical products which are curative while vaccines are preventive
- Larger number of people are exposed to vaccines
- Tolerance of vaccines ,given to healthy infants is lower than products given to the sick
- This requires investigation into the possible causes of rare AEs to vaccines as compared to other pharmaceutical products

# The Importance of Vaccine Safety Contd...

- Studies of rare events are less likely to provide definitive conclusions
- Attributable risk of 1 per $10^5$ is on the margin epidemiologically
- Vaccine safety studies have narrow margins for error
- Vaccines cannot be substituted like other drugs
- An erroneous association can undermine confidence in a vaccine and affect National programs adversely

# Vaccine Safety – Monitoring Methods

- Vaccines undergo extensive safety and efficacy evaluations before licensure
- Phase I trials include less than 20 subjects, can detect common adverse events
- Phase II trials comprise of 50 to several hundred subjects and when conducted carefully, relationship between concentration of antigen, vaccine components, formulation techniques, effect of successive doses and reactogenicity profile can be ascertained
- For phase III clinical trials, sample size is based on efficacy considerations and inferences on safety are drawn to the extent possible during observation of < 30 days (Rosenthal K.L., 1993)

# Vaccine Safety – Monitoring Methods Contd...

- This means that only observations of common and systemic reactions are possible whether done in comparison with a placebo or double-blinded
- Better standardization of safety evaluations in phase III trials are required so that safety data across trials and vaccines can be compared
- In a phase III trials, in infants with DTaP, a standard case definition was developed for efficacy but not for safety
- Definitions of high fever varied between 39.5°c to 40.5°C (Oral vs. Rectal) and time after vaccination (48 vs. 72 hrs.)

# Vaccine Safety – Monitoring Methods Contd...

- Major differences in rates of HHEs with Pertussis vaccine in Swedish and Italian trials brought out the difficulty of standardizing assessment of rarer adverse events across cultures and health systems (Heijbel et al, *Dev. Biol. Stand*. 89; 101-103, 1997)
- Better assessment of vaccine safety before licensing may be needed due to methodological difficulties of assessing safety after licensing
- Fundamental to preventing safety problems is ensuring that vaccines are made under GMP with pre-release lot testing for safety and potency preferably parallel to clinical trials before licensure
- Immunization staff required to be trained in vaccine storage, handling and safe injection practices

# Post Licensing Surveillance

- Is critical to detect delayed onset reactions
- Or reactions in sub-populations not detected earlier
- Passive surveillance
- Recently, phase IV trials and large linked databases (LLDBS) have been added to improve methodological capabilities to assess rare risks of specific immunizations (Chen, R.T., 1994)
- Variation in rates of adverse events and immunogenicity by manufacturer or even lot might be possible (Baraff I. J. Paediatrics, 1984)

# Post Licensing Surveillance Contd...

- Observational studies pose methodological difficulties
- Prone to ascertainment bias
- It is difficult to control individuals who do not receive a vaccine due to contraindication or low socio-economic status
- Such individuals may have a different risk for an ADR, than vaccinated individuals
- Seizures or SIDS may be more common in unvaccinated (VACCINE, 3rd edition, 1147, 1999)

# Post Licensing Surveillance Contd...

- In developing countries, there is increasing recognition of importance of adverse events due to program failure, than inherent properties of vaccine (WHO, Wkly. Epidemiol. Rec. 71, 237-41, 1997)
- Reconstitution with wrong diluent , TSS With Measles Vaccine..
- Contaminated needles or syringes.
- In Zimbabwe, switch of strain in BCG vaccine - lymphadenitis outbreak
- Problems with intra-dermal techniques.
- Constant vigilance for mothers/children required to be kept by health personnel.

# Spontaneous Reporting Systems

- Passive surveillance
- Cornerstone of vaccine safety monitoring
- Low cost
- System in place for all drugs including vaccines in U.K., Sweden, France, New Zealand
- In many developing countries, WHO(EPI) - MOH, administer all vaccines and adverse events are first reported to health care providers (workers)
- Many countries have different systems for vaccines as Canada, Denmark, India, U.S.A. and Brazil

# Reporting Systems

- VAERS (U.S.A.)
- MSAEFI (CDC), U.S.A.
- VAAE (CANADA)
- IMPACT (CANADA)
- YELLOW CARD REPORTING SYSTEM (U.K.)
- BCDSP (U.S.A.)
- ABERDEEN DUNDEE MONITORING SYSTEM (SCOTLAND)
- PRESCRIPTION EVENT MONITORING (DSRU, SOUTHAMPTON, U.K. )
- ICMR (NEW DELHI, INDIA)
- UPPSALA (SWEDEN)

# VAERS

- VAERS, established in 1988 to comply with the National Childhood Vaccine Injury act of 1986 in USA for all licensed vaccines.
- Operational since 1st November, 1990.
- Joint CDC & FDA initiative.
- Initial reportable events for DTP/Polio :
- Anaphylaxis (Within 24 hours)
- Encephalopathy ( within 7 days)
- HHE Or Shock (Within 7 days)
- Seizures ( No time limit)
- Death

# VAERS

- Reportable events MMR vaccine:
- Anaphylaxis ( within 24 hours)
- Encephalopathy ( within 15 days)
- Residual seizure disorder within 15 days , or 3 days or 2 seizures without fever or with fever < 102 Deg C Within 1 year of vaccine receipt.
- For OPV:
- Paralytic Polio within 30 days in healthy, 6 months in immunodeficient.
- For IPV- Anaphylaxis within 24 hours.

# VAERS

- Vaccines undergo extensive preclinical and clinical evaluation , with Placebo or comparator hence it is possible to pinpoint local or systemic ADRs. However VAERS lacks a control group hence clinical events are termed AEs as causality assessment is not possible.
- Sensitivity for detecting Uncommon or rare AEs is low.
- Continuous PMS is needed to identify such events.

# Post Marketing Surveillance

- PMS can be done in several ways:
- Vaccine lots are tested for potency, safety, sterility,purity,identity,constituents prior to release.
- After licensure Vaccine is monitored through a well planned Phase IV protocol.
- OR Collection of spontaneous reports from VAERS or medical literature provide an affordable, ongoing means of detecting new adverse events.

# Pros & Cons of VAERS

- Sentinal for detection of previously unreported Vaccine AEs or unusual increase in reported events.
- Useful for newly licensed vaccines, new indications of previous vaccines.
- Gives number of adverse events nationally
- Examines risk factors for AEs
- Provides Vaccine specific AE data.
- Relatively inexpensive.
- No Laboratory or clinical data?

# Weaknesses

- Dose distribution data not available.
- No comparator group hence causality assessment is limited.
- Under-reporting.
- Inadequate information by reporter.
- Passive surveillance.
- Biased reporting??

# LLDBs

- Post licensure studies are expensive and test limited hypothesis.
- Large Link Databases are a promising approach for pharmaco-epidemiological studies.
- Derived from defined populations like universal health care systems, information on Exposure & outcomes is available.
- Under-reporting & bias are minimized.
- Denominator data are available.
- DTP & SIDS. MMR & seizures. Etc.

# Vaccine Safety Datalink (CDC)

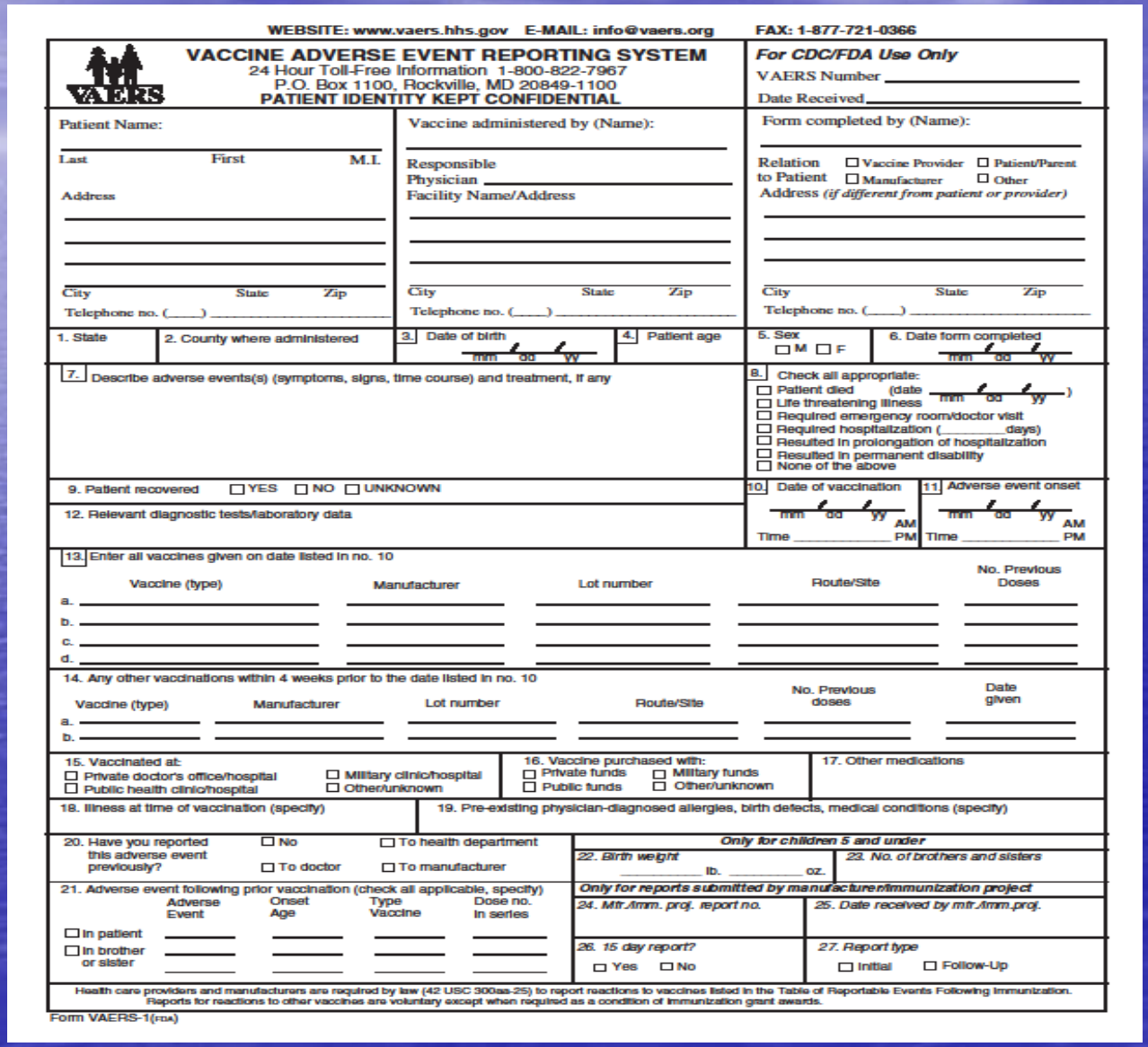
- Collaboration between CDC and 9 large HCOs in USA.
- 500,000 cohorts 0-6 years are linked to conduct safety analysis based on reports

  in literature or concerns from VAERS.
- Provide information to Committees.
- Rapid cycle analysis ( active surveillance) is done every 4 weeks between vaccinated & unvaccinated cohorts to compare AE profile. Eg Pentacel, Kinrix,Rotavirus, 2009 AH1N1 vaccine.

# Vaccine Safety Datalink

- The main aim is to conduct valid, accurate safety studies.
- A new tool to detect early signs of vaccine AEs.
- An increase in Intussusception was detected after 2589 doses about the same time reports were submitted to VAERS for Rotateq.
- Allows rapid & routine population based assessment of new vaccine safety.
- ( Davis RL et al, Epidemiology, 2005,16(3) :336-341)

# VAERS Form



WEBSITE: www.vaers.hhs.gov E-MAIL: info@vaers.org FAX: 1-877-721-0366

**VACCINE ADVERSE EVENT REPORTING SYSTEM**
24 Hour Toll-Free Information 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
**PATIENT IDENTITY KEPT CONFIDENTIAL**

*For CDC/FDA Use Only*
VAERS Number _____
Date Received _____

Patient Name:
Last First M.I.
Address
City State Zip
Telephone no. (____) _____

Vaccine administered by (Name):
Responsible Physician _____
Facility Name/Address
City State Zip
Telephone no. (____) _____

Form completed by (Name):
Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other
Address *(if different from patient or provider)*
City State Zip
Telephone no. (____) _____

1. State | 2. County where administered | 3. Date of birth mm dd yy | 4. Patient age | 5. Sex ☐ M ☐ F | 6. Date form completed mm dd yy

7. Describe adverse events(s) (symptoms, signs, time course) and treatment, if any

8. Check all appropriate:
☐ Patient died (date mm dd yy)
☐ Life threatening illness
☐ Required emergency room/doctor visit
☐ Required hospitalization (_____days)
☐ Resulted in prolongation of hospitalization
☐ Resulted in permanent disability
☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

10. Date of vaccination mm dd yy Time _____ AM PM

11. Adverse event onset mm dd yy Time _____ AM PM

12. Relevant diagnostic tests/laboratory data

13. Enter all vaccines given on date listed in no. 10

| | Vaccine (type) | Manufacturer | Lot number | Route/Site | No. Previous Doses |
|---|---|---|---|---|---|
| a. | | | | | |
| b. | | | | | |
| c. | | | | | |
| d. | | | | | |

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

| | Vaccine (type) | Manufacturer | Lot number | Route/Site | No. Previous doses | Date given |
|---|---|---|---|---|---|---|
| a. | | | | | | |
| b. | | | | | | |

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other/unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

21. Adverse event following prior vaccination (check all applicable, specify)

| | Adverse Event | Onset Age | Type Vaccine | Dose no. in series |
|---|---|---|---|---|
| ☐ In patient | | | | |
| ☐ In brother or sister | | | | |

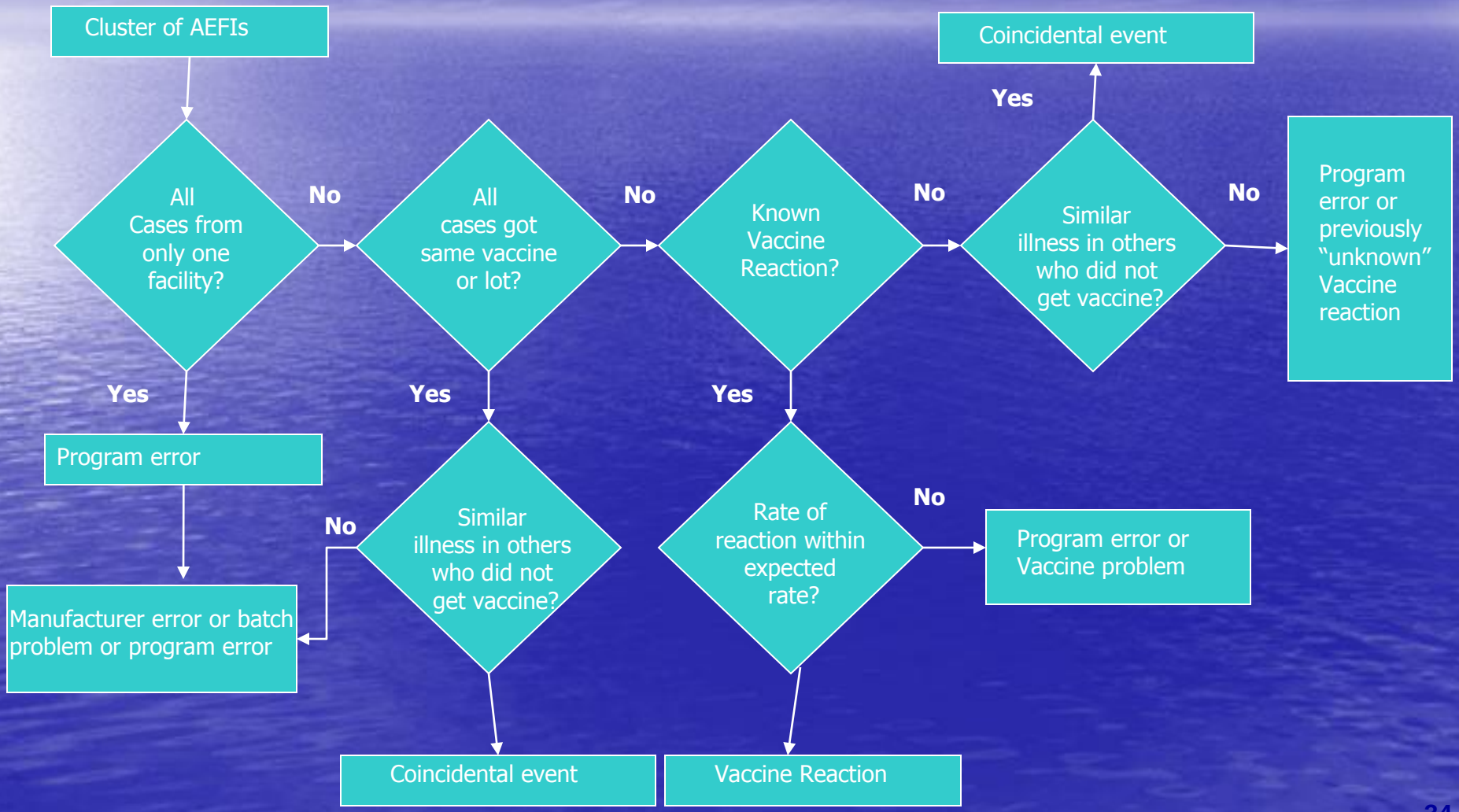
*Only for children 5 and under*
*22. Birth weight* _____ lb. _____ oz.
*23. No. of brothers and sisters*

*Only for reports submitted by manufacturer/immunization project*
*24. Mfr./imm. proj. report no.*
*25. Date received by mfr./imm.proj.*
*26. 15 day report?* ☐ Yes ☐ No
*27. Report type* ☐ Initial ☐ Follow-Up

Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.

Form VAERS-1(FDA)

# Steps for Identifying the Most Likely Cause of a Cluster of AEFIs



# The Four Elements

- **MINIMUM INFORMATION** requested to report an Adverse Event *(ICH/FDA)*
  - An identifiable source
  - An identifiable patient
  - An identifiable product
  - An Adverse Event or fatal outcome

# Seriousness

**Serious Adverse Event *(CPMP/PhVWP/108/99)***

- This includes an adverse reaction which falls into one or more of the following categories:
  - Fatal
  - Life-threatening
  - Results in persistent or significant disability, incapacity
  - Results in or prolongs hospitalisation
  - Congenital anomalies/birth defects
- Other: Medical judgment should be exercised in deciding whether a reaction is serious in other situations. Important adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient should be considered as serious.

# Expectedness

- **Unexpected Adverse Reaction** (CPMP/PhVWO/108/99)

  This is an adverse reaction which is not specifically included as a suspected adverse effect in the Summary of Products Characteristics (SPC). **This includes any adverse reaction whose nature, severity or outcome is inconsistent with the information in the SPC.**

It also includes class-related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product.

# Company Core Data Sheet

- **CDS (ICH E2C step 5 nov. 2000)**

  A document **prepared by the marketing authorisation holder** (MAH), containing in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

# What is Vaccinovigilance ?

- **VACCINE PHARMACOVIGILANCE**

  **" is defined as the 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 »**

  *WHO/CIOMS Working group on vaccine Pharmacovigilance 2007*

# Cluster

A number of ***n*** **cases** of Adverse Events reported after administration of the **same vaccine**, coming from the **same lot** or/and from the **same area** or/and from the **same source**
(i.e.: same physician) during a **short period of time** (*at the same time or within less than a month).*

# Definitions: Brighton Collaboration

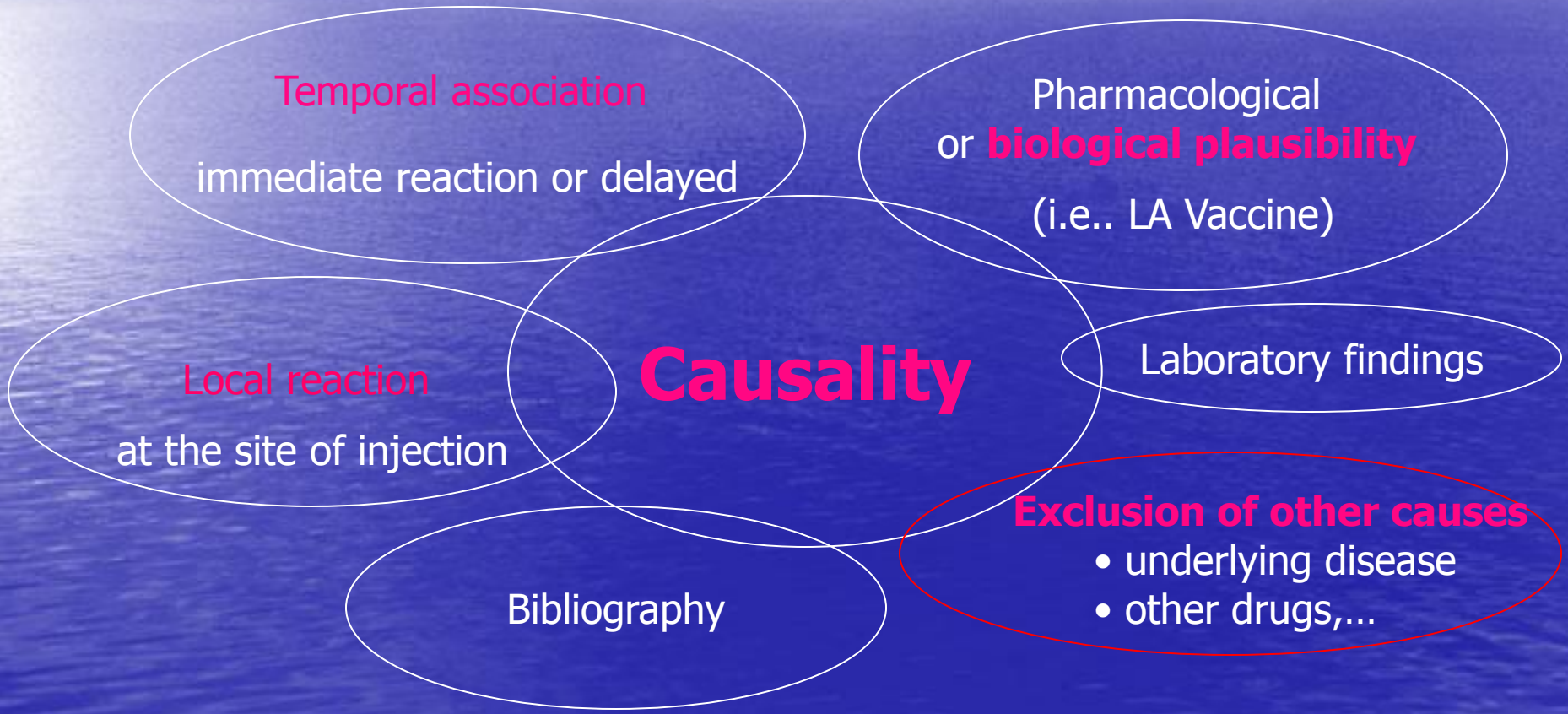
- The Brighton collaboration was initiated in 1999 at Brighton (UK) during an EVM meeting due to a lack of international definitions for AEFI.
- The Brighton Collaboration is an international voluntary collaboration to facilitate the development, dissemination and evaluation of high quality information about the safety of human vaccines.

http://brightoncollaboration.org

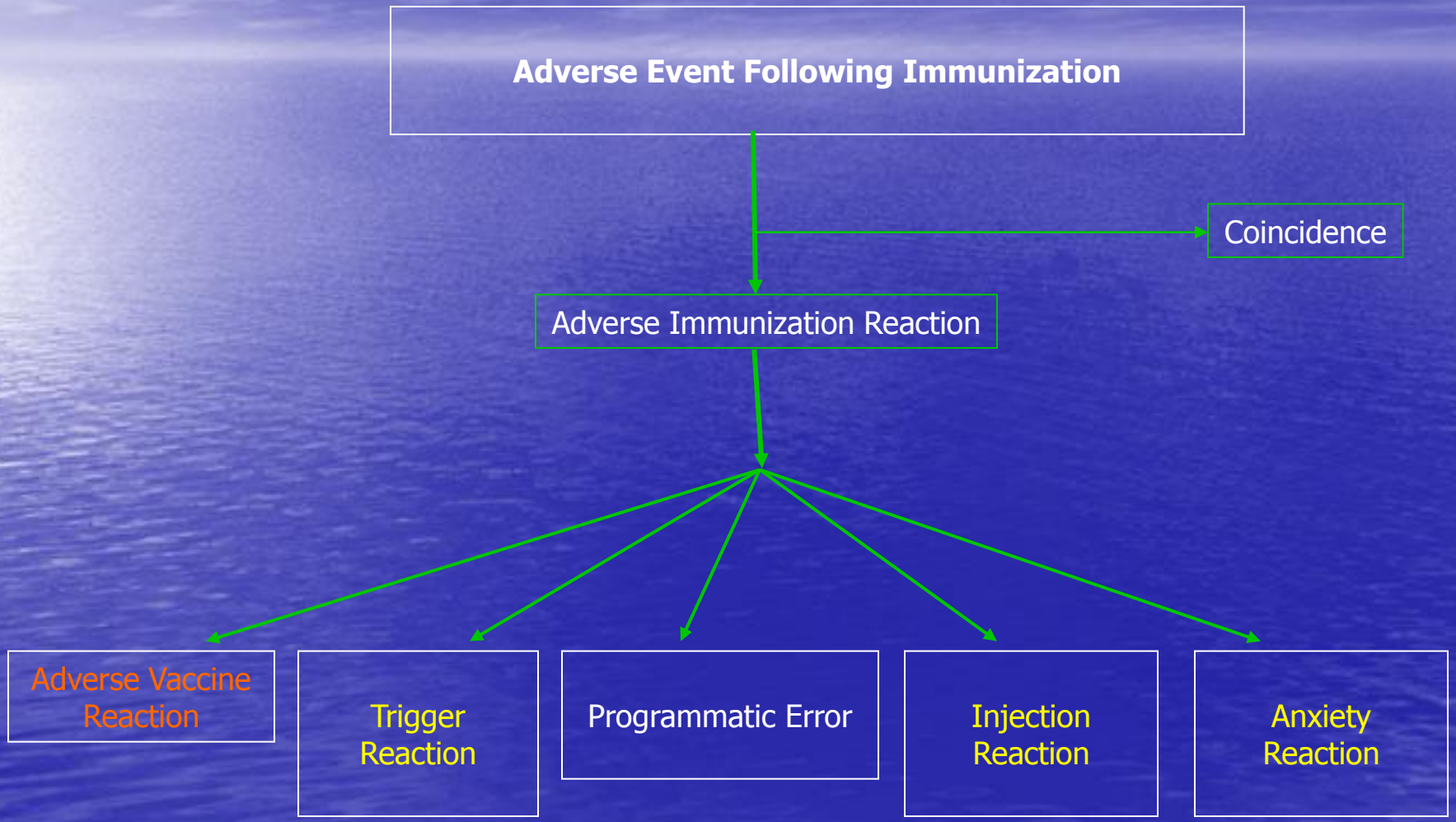
# Brighton Collaboration Case Definitions and Guidelines

| Developed | Developed | In progress Planned |
|---|---|---|
| Fever<br>Hypotonic-Hyporesponsive Episode (HHE)<br>Intussusceptions<br>Nodule at injection site<br>Abscess, induration, swelling<br>Pruritus, cellulitis<br>Persistent crying<br>Seizure<br>SUDI<br>Aseptic meningitis, Encephalitis<br>Thrombocytopenia | CFS<br>Fatigue<br>Smallpox AEFI:<br>Generalized Vaccinia<br>Inadvertent inoculation<br>Eczema vaccinatum<br>Rash<br>Local reaction | Myalgia<br>Paresthesia<br>Urticaria<br>Bell's palsy<br>GBS<br>ORSS<br>Flu like syndrome<br>Neo natal AEFI |

# Causality Assessment



# AEFI


Adverse Event Following Immunization
Coincidence
Adverse Immunization Reaction
Adverse Vaccine Reaction
Trigger Reaction
Programmatic Error
Injection Reaction
Anxiety Reaction

# CIOMS1 Form

CIOMS FORM

**SUSPECT ADVERSE REACTION REPORT**

**I. REACTION INFORMATION**

| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH DA | MO | YR | 2a. AGE YRS | 3. SEX | 4-6 REACTION ONSET DA | MO | YR | 8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION: |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | [] PATIENT DIED<br>[] LIFE THREATENING<br>[] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION<br>[] INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY<br>[] CONGENITAL ANOMALY<br>[] OTHER MEDICALLY IMPORTANT CONDITION |

7.- 13. DESCRIBE REACTION(S) *(including relevant tests/lab data)*

**II. SUSPECT DRUG(S) INFORMATION**

| 14. SUSPECT DRUG(S) *(include generic name)* | | 20. DID EVENT ABATE AFTER STOPPING DRUG? [] YES [] NO [] NA |
|---|---|---|
| 15. DAILY DOSE | 16. ROUTE OF ADMINISTRATION | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 17. INDICATIONS FOR USE | | [] YES [] NO [] NA |
| 18. THERAPY DATES *(From/To)* | 19. THERAPY DURATION | |

**III. CONCOMITANT DRUGS AND HISTORY**

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat event)*

23. OTHER RELEVANT HISTORY

**IV. MANUFACTURER**

| 24a. NAME AND ADDRESS OF MANUFACTURER<br>SANOFI PASTEUR SA<br>2 avenue du Pont Pasteur<br>69367 LYON Cedex 07<br>FRANCE | | |
|---|---|---|
| | 24b. MFR. CONTROL NO. | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE<br>[] STUDY [] LITERATURE<br>[] AUTHORITY<br>[] HEALTH PROFESSIONAL<br>[] OTHER | |
| DATE OF THIS REPORT | 25a. REPORT TYPE<br>[] INITIAL [] FOLLOW UP [] FINAL | |

24b. MFR/CPVD Number

24d. REPORT SOURCE
[] STUDY [] LITERATURE
[] HEALTH PROFESSIONAL
[] HEALTH AUTHORITY

25a REPORT TYPE
[] INITIAL [] FOLLOW UP

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

[] PATIENT DIED

[] INVOLVED OR PROLONGED INPATIENT HOSPITALISATION

[] INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY

[] LIFE THREATENING

[] OTHERS

# Risk Management Plan

- Set of Pharmacovigilance activities and interventions designed to
  - Identify
  - Characterize
  - Prevent
  - Or minimize

  Risks relating to medicinal products , including the assessment of the effectiveness of those interventions

  *(Article 34 of EC regulations N° 1901/2006)*

*A risk minimization plan should be provided if needed*

# AEs Frequency

| Type | Frequency | |
|---|---|---|
| Very Frequent | > 10% | C T |
| Frequent/ Common | 1% - 10% | |
| Infrequent/ uncommon | 0.1% - 1% | |
| Rare | 0.01% - 0.1% | P M S |
| Very Rare | 0.001%- 0.01% | |
| Exceedingly Rare | <0.001% - < 1x 10^6 | |

# Websites

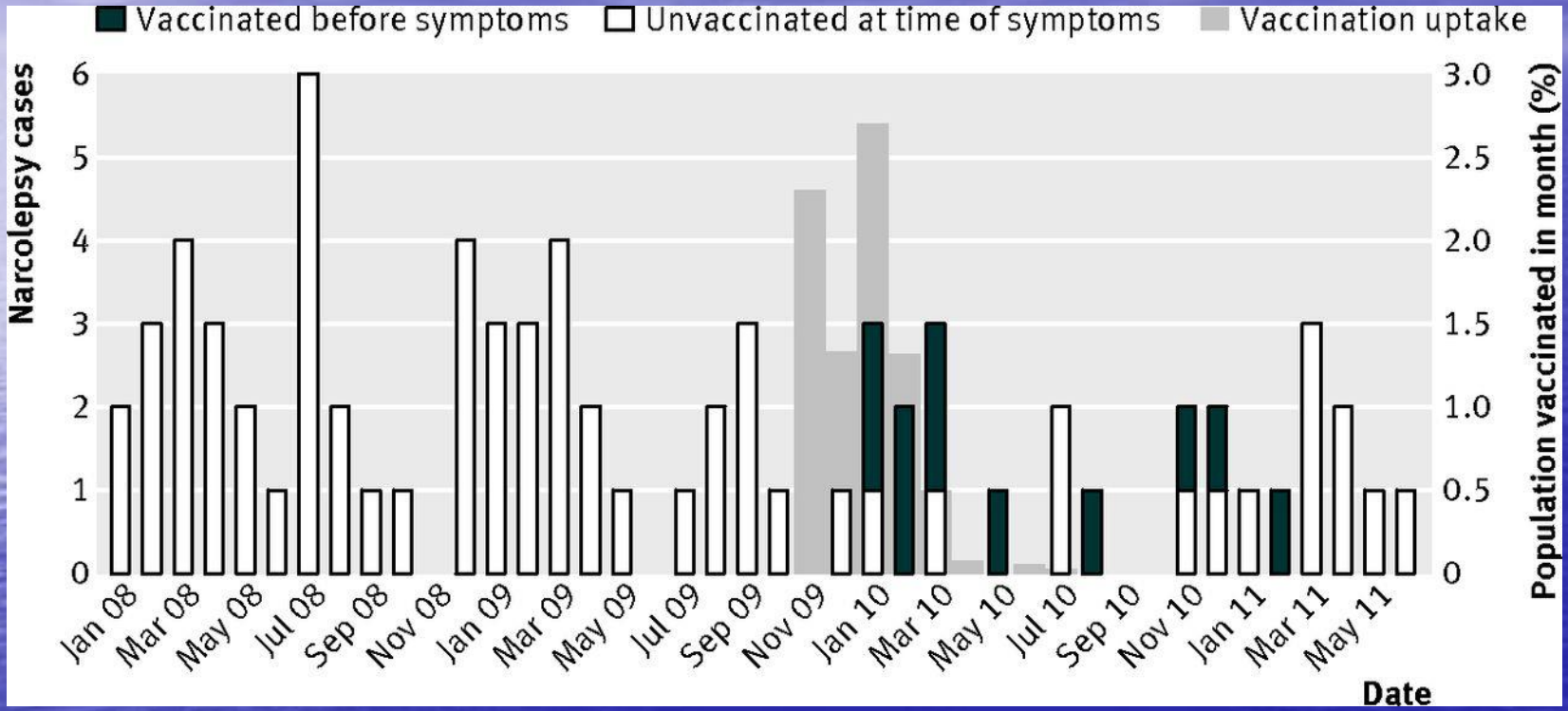
- ICH - http://www.ich.org
- CIOMS - http://www.cioms.ch/index.html
- EMEA - http://www.emea.eu.int/index/indexh1.htm
- CDC - http://www.cdc.gov/
- WHO - http://www.who.int/en/
- AFSSAPS - http://agmed.sante.gouv.fr/
- BRIGHTON COLLABORATION - http://www.brightoncollaboration .org
- EFPIA :http://www.efpia.org/
- IOM: http://www.iom.edu/

# Case Study

- **Objective:** To evaluate the risk of narcolepsy in children and adolescents targeted for vaccination with ASO3 adjuvanted pandemic A/H1N1 2009 vaccine .
- **Design:** Retrospective analysis. Clinical information and results of sleep tests were extracted from hospital notes between August 2011 and February 2012 and reviewed to confirm the diagnosis. Vaccination and clinical histories (GPs).
- **Setting:** Sleep centres and paediatric neurology centres in England.
- **Participants:** age group 4-18 with onset of narcolepsy from January 2008 for one year.
- **Main outcome measures:** The odds of vaccination in those with narcolepsy compared with the age matched English population after adjustment for clinical conditions that were indications for vaccination. The incidence of narcolepsy within six months of vaccination compared with the incidence outside this period measured with the self controlled cases series method.

- **Results:** Case notes for 245 children and young people were reviewed; 75 had narcolepsy (56 with cataplexy) and onset after 1 January 2008. Eleven had been vaccinated before onset; seven within six months. In those with a diagnosis by July 2011 the odds ratio was 14.4 (95% confidence interval 4.3 to 48.5) for vaccination at any time before onset and 16.2 (3.1 to 84.5) for vaccination within six months before onset. The relative incidence from the self controlled cases series analysis in those with a diagnosis by July 2011 with onset from October 2008 to December 2010 was 9.9 (2.1 to 47.9). The attributable risk was estimated as between 1 in 57 500 and 1 in 52 000 doses.

# Figure 2. Number of cases of narcolepsy by month and year of onset according to vaccination status at onset.




Elizabeth Miller et al. BMJ 2013;346:bmj.f794

- **Conclusion:** The increased risk of narcolepsy after vaccination with ASO3 adjuvanted pandemic A/H1N1 2009 vaccine indicates a causal association, consistent with findings from Finland. Because of variable delay in diagnosis, however, the risk might be overestimated by more rapid referral of vaccinated children.
- EMA restricted use of Pandmerix in subjects younger than 20 years.
- Seasonal influenza vaccines have not been linked to Narcolepsy.
- The cause of narcolepsy may have been the AS03 adjuvant which contains squalene (oil emulsion), alpha-tocopherol and polysorbate.
- However, the vaccine is still licensed and being used in several countries worldwide.

# THANK YOU

# Let us meet again..

We welcome you all to our future conferences of OMICS International

5th International Conference & Exhibition on Pharmacovigilance & Clinical Trials

On

September 19 - 21, 2016 at Vienna, Austria

http://pharmacovigilance.pharmaceuticalconferences.com/