P95

TURNING DATA
INTO EVIDENCE

An introduction to pharmacovigilance and vaccine safety

www.p-95.com

Module content

- What is pharmacovigilance and why do we need it?
- Key definitions
- Global standards in pharmacovigilance
- The specific challenges of vaccine pharmacovigilance
- World Health Organization (WHO) perspectives
- Immunisation programmes
- How vaccines cause side effects
- Data sources and evidence hierarchy
- Key steps in pharmacovigilance, for vaccines
- Proactive pharmacovigilance planning

Pharmacovigilance

- *World Health Organization (WHO) - "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem"*.

- Key objectives –

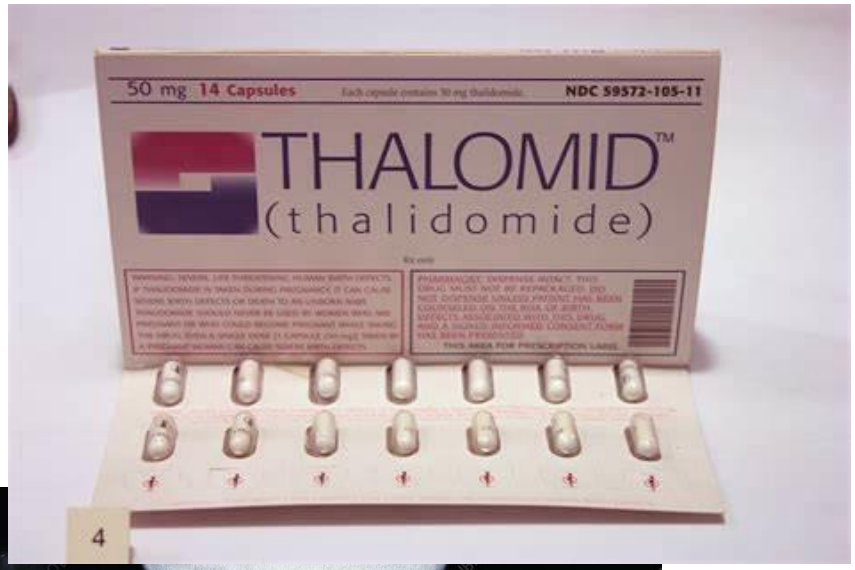
  - to prevent harm from adverse reactions

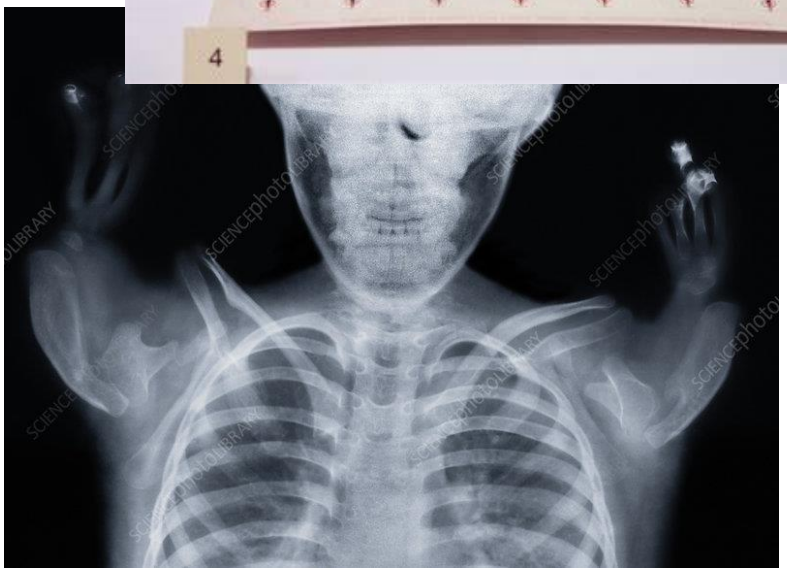
  - to promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public

- Applies equally to vaccines and medicines

Why we need pharmacovigilance (PhV)

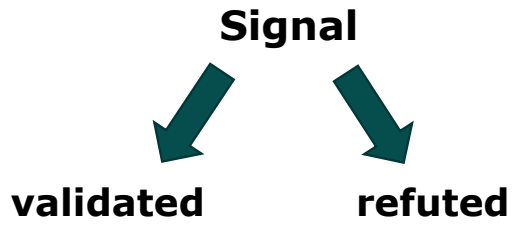
- No medicine is without risk, and safety signals need to be;
  - detected as early as possible
  - confirmed
  - quantified
  - so that action can be taken to minimize risk and optimise risk:benefit balance
  - communicated so that health professionals and patients can make informed decisions





Why we need pharmacovigilance (PhV)

- But PhV is not just about detecting new risks and is not just a process
  - it's a science, and is therefore about optimizing the way we obtain and use data to make evidence-based decisions




daughters vaccinated, others are adamant that it has triggered alarming side-effects . . .

HOW SAFE IS THE CERVICAL CANCER JAB?

by Rachel Porter

began. It was the summer holidays when she first noticed that Carly, her eldest daughter, was seriously out of sorts.

'Anyone who knew Carly before will tell you what a chatterbox she was. She had so much energy she

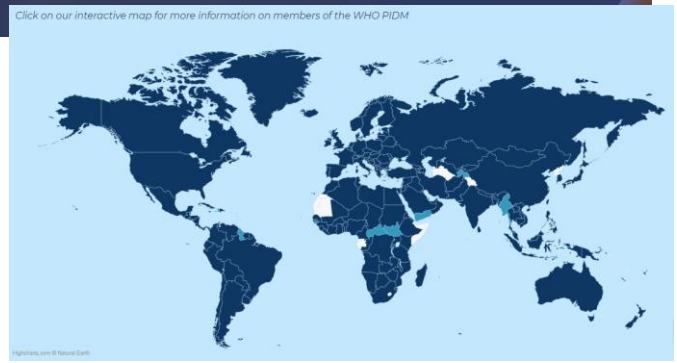

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 November 2015
EMA/714950/2015

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

PhV – a global system



ICMRA
International Coalition of Medicines Regulatory Authorities

ICH
harmonisation for better health

ICH

INTERNATIONAL COUNCIL FOR HARMONISA
of
Technical Requirements
for Pharmaceuticals for Human Use

- Unique harmonisation initiative for regu… and pharmaceutical industry
- Originally founded in 1990
- Reformed as a non-profit legal entity under Swiss Law on 23 October 2015

CIOMS

PHARMACOVIGILANCE

Uppsala Monitoring Centre

AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

African Union Smart Safety Surveillance (AU-3S)

Global vaccine safety blueprint

Immunization, Vaccines and Biologicals

World Health Organization

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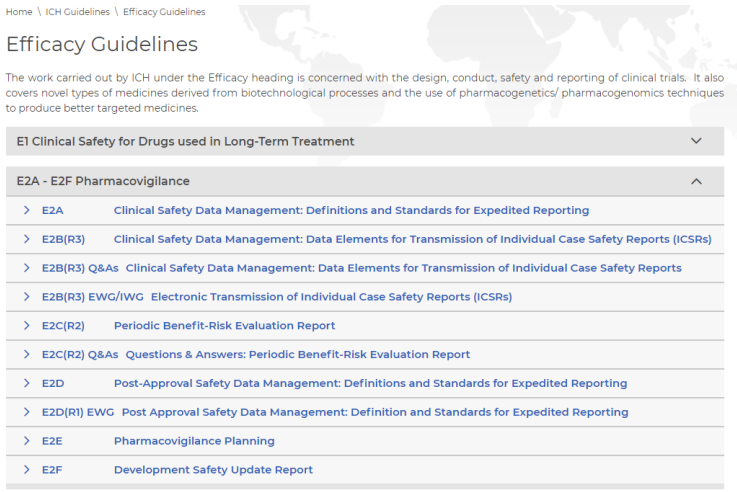
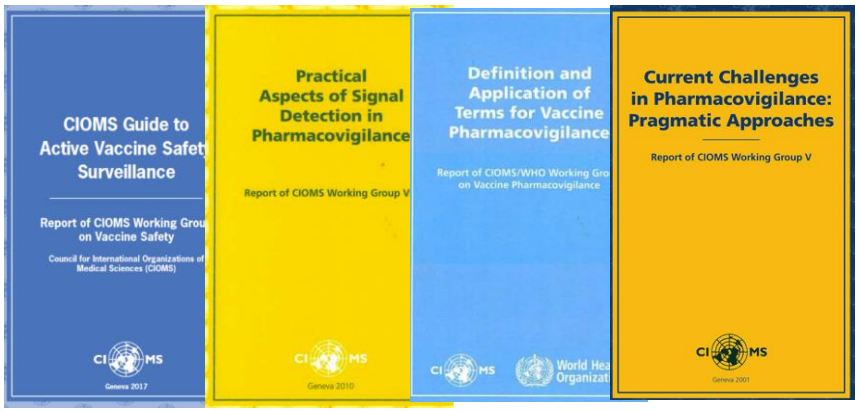
PhV – standardization

- Many of the same products are on multiple, global markets
- Need to avoid duplication of effort and discordant/competing PhV requirements
- International Council for Harmonisation (ICH) – since 1990 has developed guidelines to standardize and harmonise regulatory requirements
  - Guidelines E2A-E2F – Pharmacovigilance (amongst other guidelines on data standards)



- Council for International Organizations of Medical Sciences (CIOMS) - has published a range of PhV guidance to foster best practices at global level



Key definitions I*

- **Adverse event (AE)** - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and **which does not necessarily have to have a causal relationship** with this treatment.

- **Adverse drug reaction (ADR)** - A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function

    - "response" means that a causal relationship between a medicinal product and an adverse event is **at least a reasonable possibility**
    - in regulatory terms, ADR also applies to vaccines (i.e. **vaccine=drug** in this context)
    - not *proven* reactions - usually termed *'suspected'* ADRs

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* ICH E2A -Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

Key definitions II*

- **Serious AE (SAE)/Serious ADR** – an AE/ADR that results in death, is life-threatening (at the time of the event), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
  - ***Serious is different to severe*** (e.g. a severe headache might be intense and affect tolerability, but not necessarily 'serious' in regulatory terms)

- **Expected ADR** - nature or severity is consistent with that included in the appropriate reference safety information (e.g. Investigator's brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

- **Suspected unexpected serious adverse reaction (SUSAR)** – an ADR that is both serious and unexpected (clinical trials)

- **Individual case safety report (ICSR)** - this refers to the ***format and content*** for the submission of an individual report of suspected adverse reactions to regulatory authorities - a valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction, and at least one suspect medicinal product

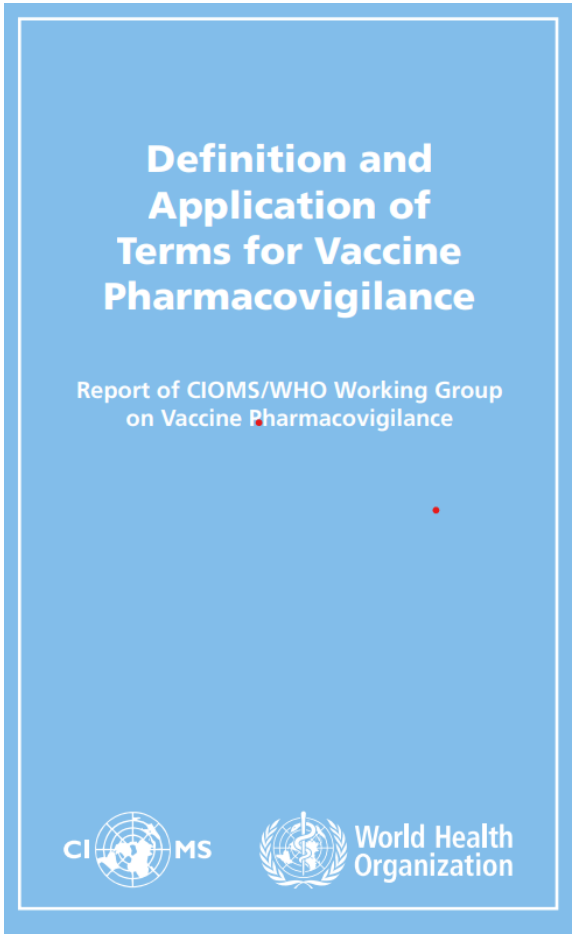
* ICH E2A -Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

Key definitions III

- **Adverse event of special interest (AESI)** – an event that a sponsor may wish to closely monitor in clinical trials or worthy of specific vigilance in post-marketing. Such events should be described in protocols of PhV plans.

- **Adverse event following immunization (AEFI)** - any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.

- AESI terminology generally used in study protocols/PhV plans, and AEFI terminology is used in WHO guidance, but **these are not regulatory/legal definitions and are not distinct from AEs/ADRs**

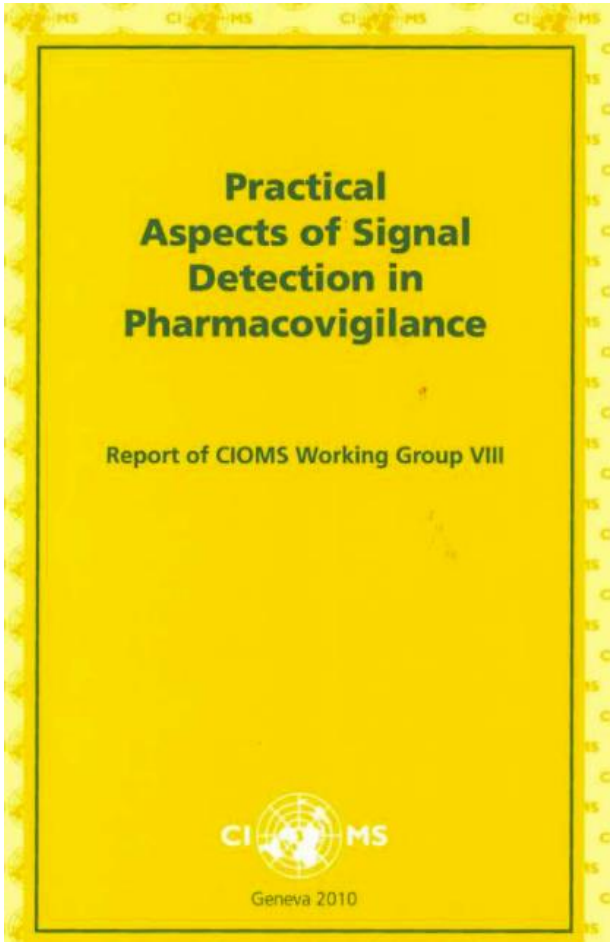


https://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf

Key definitions IV

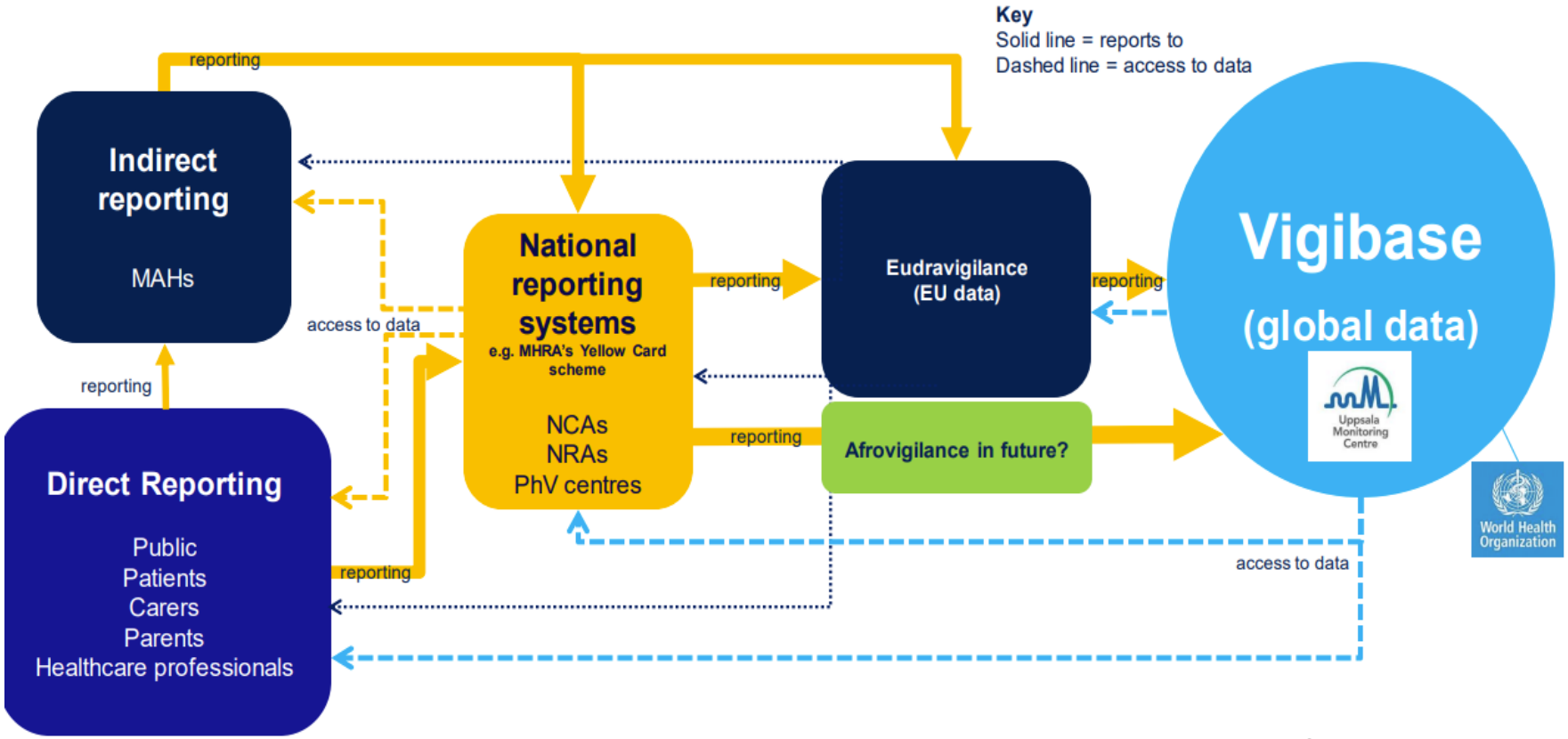
- **Signal** – "*Information that arises from one or multiple sources (including observations and experiments) which suggests a new **potentially** causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify **verificatory** action"*

  - *may originate from 'non-clinical data to a single AE/ADR report to the findings from a large epidemiological study' – but regardless of source it is, essentially, something that requires more analysis to determine the validity and strength of the 'signal'*



https://cioms.ch/publications/product/practical-aspects-of-signal-detection-in-pharmacovigilance-report-of-cioms-working-group-viii/

Global reporting of ICSRs (ADRs)



Source - MHRA

WHO AEFI guidance

- **A1. Vaccine product-related reaction**: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
- **A2. Vaccine quality defect-related reaction**: An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer.
- **A3. Immunization error-related reaction**: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and that thus, by its nature, is preventable.
- **A4. Immunization anxiety-related reaction/Immunization stress related response (ISRR):** An AEFI arising from anxiety about the immunization.
- **C. Coincidental event:** An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety

Adverse events following immunization (AEFI) (who.int)

WHO - Causality

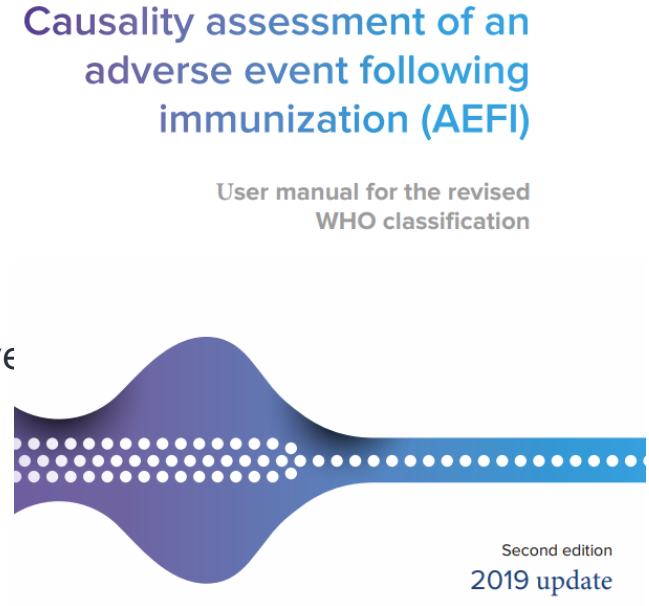
- Causality assessment occurs at two levels;
  - Individual case – 'did the vaccine cause it?'
  - Population level – 'can the vaccine cause it?'

- 'Can it?' requires an assessment of the totality of available data, particularly for events that can occur naturally

- Assigning one of the five AEFI categories is an individual-leve judgement
  - 'it can' does not necessarily mean 'it did'

- Very few examples when individual cases have proven causality (e.g. isolation of live vaccine virus in affected organ/tissue, a novel syndrome with confirmed biomarkers etc)
    - 'A1' classification is mostly a judgement of probability/possibility than certainty
      - 'it did' does not always mean 'it can' (the same applies to SUSAR reports)

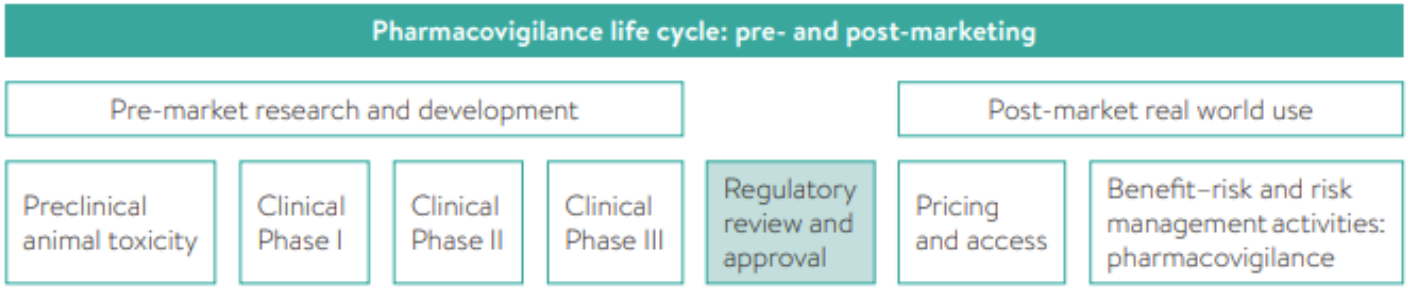
        - in most cases, individual-level causality judgements are just a part of the signal detection process and/or used for determining 'reportability' (i.e. whether SUSAR, ADR)



https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/aefi

PhV – vaccines vs drugs

- Do we need to treat vaccines any different to drugs in pharmacovigilance?



Source - www.who.int/hiv/pub/10.pdf

- The underpinning principles are the same……

  - non-clinical studies have limited predictive value for safety in humans
  - clinical trials are limited in size, duration, generalisability
    - can only detect risks within confines of those limitations
  - rare risks can only be identified/confirmed in 'real-life'
  - we need continuous, life-cycle safety surveillance and risk-benefit evaluation

PhV – vaccines vs drugs

- The general requirements, definitions and regulatory processes for the conduct of clinical trials (safety) for new vaccines are no different to medicines, notably (but not limited to):

  - ICH E2A Clinical safety data management: definitions and standards for expedited reporting | European Medicines Agency (europa.eu)
  - ICH E8 General considerations for clinical studies | European Medicines Agency (europa.eu)
  - ICH E2E Pharmacovigilance planning (Pvp) | European Medicines Agency (europa.eu)
  - E 9 Statistical Principles for Clinical Trials (europa.eu)

PhV – vaccines vs drugs

- But, unlike most drugs……

  - vaccines (mostly) given to otherwise healthy people
    - lower tolerance of risks

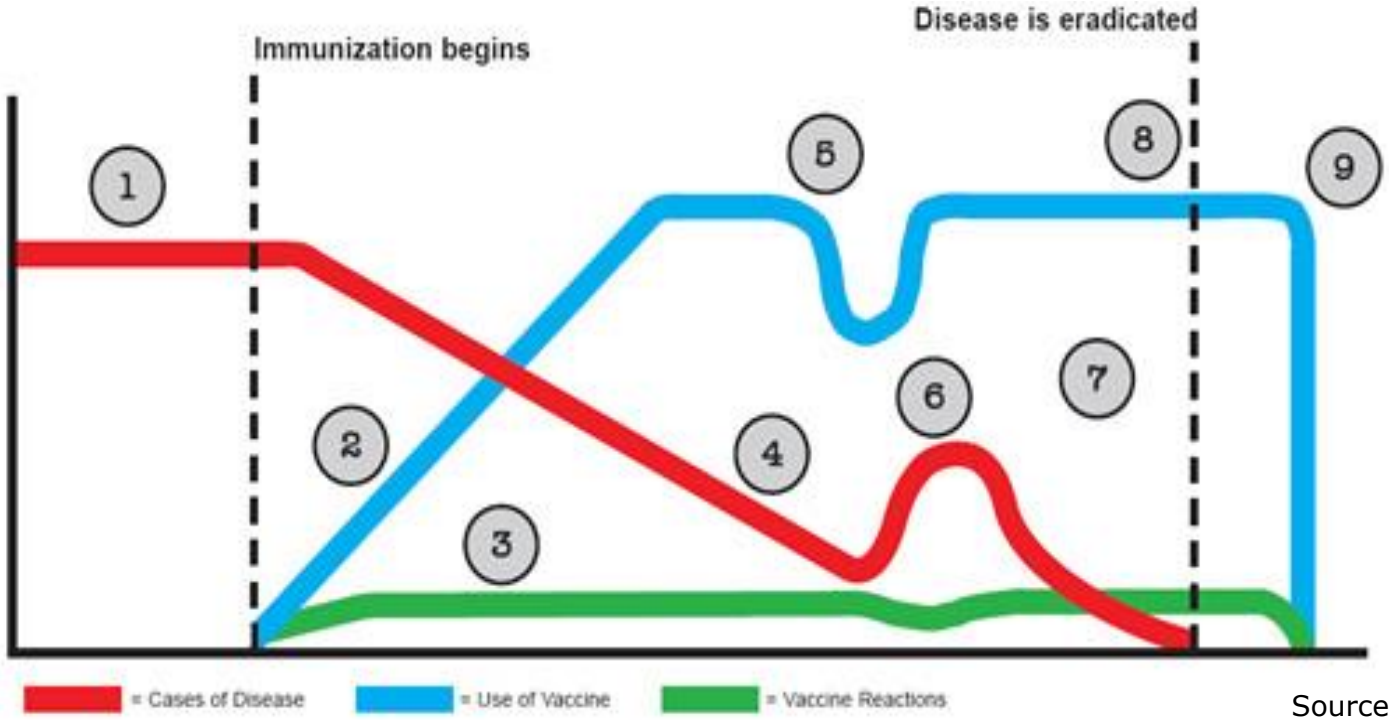
  - perception of benefits can be low
    - serious disease rare, herd immunity
    - benefits can be long-term (e.g. HPV-associated cancers)

  - given to large % of the population
    - +++ AE/ADR reports
    - very rare, SAEs/suspected ADRs are inevitable
    - lack of comparable control groups (implications for real world studies)

PhV – vaccines vs drugs

- And, unlike for most drugs……
  - Cold chain, batch-specific safety and biological variability
    - 'vaccine programme' safety is as important as product-specific safety
  - Risk/Benefit balance is dynamic
    - Temporal and geographic (e.g. oral polio)
  - Vaccine safety 'scares' can have massive impact
    - Not only on target population but on wider population – resurgence of disease
  - **So, ALL aspects of pharmacovigilance require special considerations and expertise for vaccines**

Life-cycle of a vaccine programme



Source - US CDC website

- Robust Risk Management Strategies needed to:
    - Monitor events (3) and assess risks
    - Manage vaccine confidence (5 and 6)

False vaccine safety concerns

- Pertussis vaccine and encephalopathy (1970s)
  - Resurgence in pertussis in UK
- MMR (and thiomersal-containing vaccines) and autism
  - Measles outbreaks, general vaccine confidence
- Hepatitis B vaccines and multiple sclerosis
  - Adolescent programme in France stopped
- Polio vaccines and contamination (contraceptives, HIV…)
  - Hindering the global eradication campaign
- HPV vaccine and chronic fatigue syndrome
  - Reduced vaccine uptake in some EU countries

But, vaccines CAN have real risks

- 1976 US outbreak of novel H1N1
  - 1 death - pandemic feared
- Mass immunisation programme
  ~45 million doses given

President Ford leading by example

- Campaign stopped within 3 months
  - ~ 500 cases of Guillain Barre Syndrome attributed to vaccine (10-fold increased risk) - ~25 fatal

  ……..the 1976 Pandemic did not materialise

- In recent times……..
  - 2009/10 swine flu vaccines – narcolepsy
  - COVID 19 vaccines – thrombotic syndrome, myocarditis

Immunisation programmes

- Effective PhV and Risk Management Planning for vaccines requires an understanding of…
    - the (national) immunisation programme
    - the (national) regulatory, policy and clinical framework
    - the infrastructure for delivery of the programme
    - the various stakeholders and their needs
- These aspects are broadly consistent between countries
- However, immunisation schedules can differ widely
    - Data and systems differ across countries
    - **Safety profile (and R/B) of individual vaccines may differ as a consequence**

Stakeholders in vaccine PhV

- Regulatory Authorities/National Competent Authorities
- Policy makers/public health authorities
- Pharmacovigilance Centres (if independent from above)
- WHO
- National independent expert advisory committees
- Batch release authorities
- Disease surveillance bodies
- Health professional bodies
- Vaccine recipients, parents/carers and the general public
- The national media

- **Will differ across countries**
- **All have a stake in vaccine safety and require constant information**

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How do vaccines cause adverse reactions?

- Intrinsic properties of vaccine
  - Direct effect (e.g. live virus)
  - Host response (e.g. cytokines, hypersensitivity)
- Biological/batch variation
  - Quality defect Manufacturing change
- Programme-related
  - Not intrinsic to the vaccine

Vaccine antigens and excipients

- Antigens (the 'active' ingredients)
  - Live (e.g. MMR, oral polio, varicella, yellow fever, BCG)
  - Inactivated (killed organisms) (e.g. pertussis, inactivated polio)
  - Toxoids (e.g. diphtheria, tetanus)
  - Purified proteins, polysaccharides (e.g. flu, meningitis)
  - Vector vaccines (e.g. ebola, COVID)
  - mRNA vaccines (e.g. COVID)

- Excipients (stabilisers, preservatives, manufacturing residuals)
  - gelatin, formaldehyde, thiomersal, antibiotics, egg protein

  - **All components contribute to safety profile**
  - **No two vaccines are the same**

Live, attenuated vaccines

- Unlike other vaccines for which a 'dose' of active ingredient is administered, live vaccines generally need to first replicate within body to induce immune response
  - Replicate over a particular time course (e.g. 6-11 days, measles, 17-35 days mumps)
  - Attenuated (weakened) virus cannot cause the clinical disease, but
    - Can cause mild form of disease (e.g. measles rash)
    - Can cause disseminated infection in immunocompromised
    - Some can revert to virulence (e.g. OPV)
- In terms of biological plausibility of an ADR – time-to-onset should be compatible with the biological characteristics (unless its an allergic reaction to the excipients)

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*[note, some live vaccines are non-replicating, e.g. modified vaccinia, for which these principles would not necessarily apply]

Vector and mRNA vaccines

- In the context of PhV, the key principle of vector and mRNA vaccines (unlike other vaccines) is that the 'active ingredient' is not administered directly
  - The genetic material is 'administered' to allow the body to produce the active ingredient (i.e. the protein antigens)

- So, as for replicating live vaccines, the specific biological characteristics of antigen production should be considered in causality assessment (e.g. time-to-onset)

- As for other vaccine excipients, the vehicle for the delivery of the vaccine – whether viral vector or liposome – will determine safety just as much as the active ingredient
  - e.g. adenovirus vaccines and thrombosis, PEGylated liposomal mRNA vaccine and anaphylaxis

Vaccine efficacy and effectiveness

- Efficacy evaluated in pre-licensure trials
    - Protective efficacy, i.e. protection against the disease
        - Not always feasible or necessary
    - Immunogenicity
        - Correlates of protection
            - Antibodies, T cells, other surrogate endpoints
            - E.g. pre-cancerous lesions for HPV vaccines
- Effectiveness
    - 'Real-life' use as part of a programme
    - Effect of concomitant vaccines
    - Requires national coverage and disease surveillance data
    - Important part of post-marketing surveillance

Must consider both in benefit-risk evaluation

Vaccine failures

- Vaccine failure is a safety (as well as efficacy) issue as target diseases are serious
  - Primary failure – poor/none response to initial course
  - Secondary failure – protection wanes over time
- Need good systems in place to monitor – often part of national disease surveillance programme
  - Close liaison between regulators and public health bodies required
  - Part of Risk Management Strategy

Programme related events

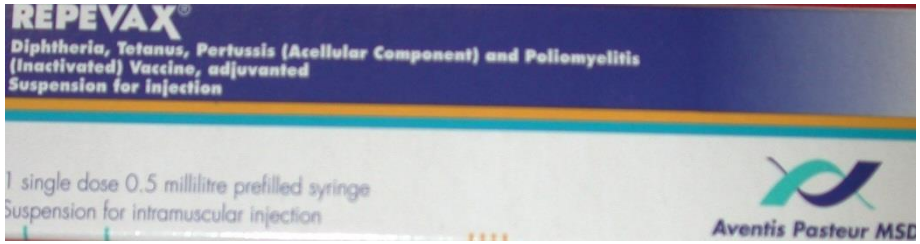
- Vaccine Sepsis due to contaminated needles/vials
- Cold chain issues
- Poor injection technique and user error
- Faints/panic attacks in fear of needle

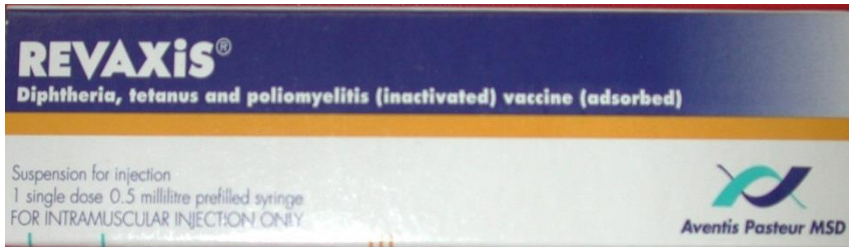
  - Not intrinsic to vaccine
  - Avoidable with good training and infrastructure

- **Mistakes happen**
- **Essential part of risk management planning**

Programme related events

- Packaging
  - Similar brands and packaging in same programme
  - Admin error reports, potential for safety/efficacy issue
  - Need to horizon scan such issues in plans





Key steps in pharmacovigilance

- Data collection
- Signal detection
- Risk assessment
- Risk-benefit/Expert advice
- Action (regulatory/other)
- Communication
- Monitor impact

  - Broad principles and methods no different to medicines

    - **However, several special considerations for vaccines**

Key steps in pharmacovigilance

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

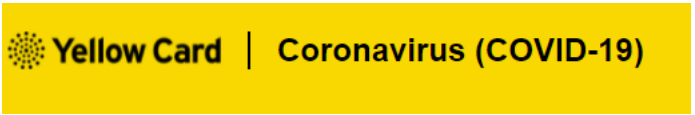
Draft finalised by the Agency in collaboration with Member States	21 February 2013
Draft agreed by ERMS FG	8 March 2013
Draft adopted by Executive Director	9 April 2013
Start of public consultation	12 April 2013
End of consultation (deadline for comments)	12 June 2013
Revised draft finalised by the Agency 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

www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/12/WC500157839.pdf

Data collection

- Some countries have specific reporting systems for vaccine ADRs
  - E.g. US VAERS

- Some have adapted systems to vaccines
  - E.g. UK Yellow Card Scheme



- Data quality and type of information required
  - Vaccine brand names (product-specific safety)
  - Batch numbers
  - Timing of vaccines, and immunisation history
  - Precise time to onset for events
  - Administration technique? (for unusual local ADRs)
  - If admin errors – explore precise reason

Signal detection

- 'Traditional' signal detection
  - Clinical evaluation of case/clusters/cumulative case series
  - More subjective
  - Look for 'index' cases, patterns/trends/consistencies
  - One [unusual/striking] case can be a 'signal'
    - With mass immunisation and high volumes of reports becomes very resource intensive

- 'Quantitative' signal detection
  - case numbers (not the narratives) to detect statistical signals
  - More objective
    - Can be automated

    - **<u>Both</u> need to be conducted in parallel**

Signal detection

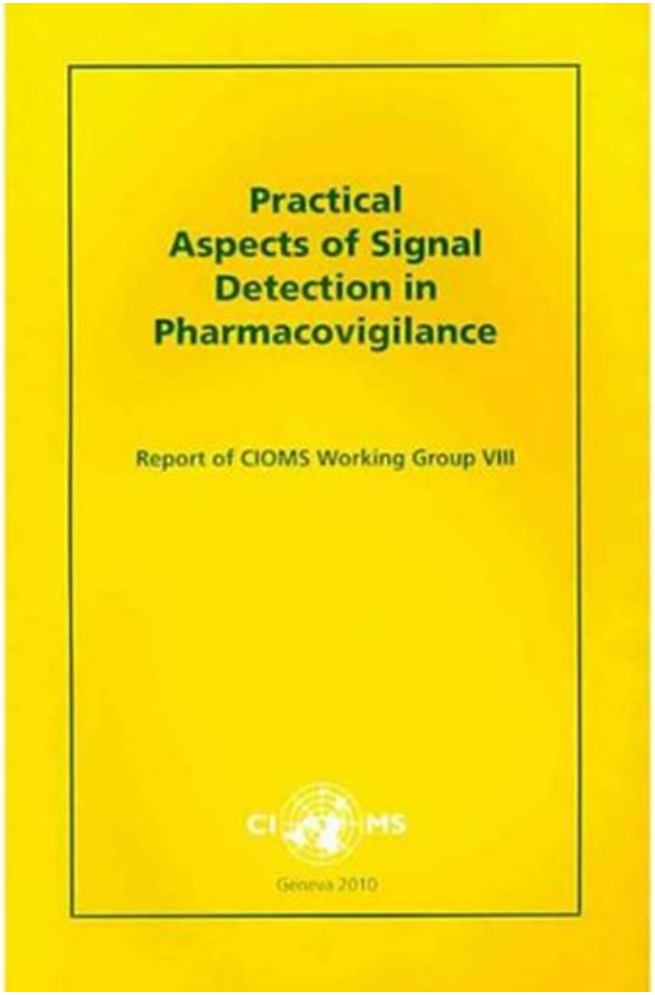
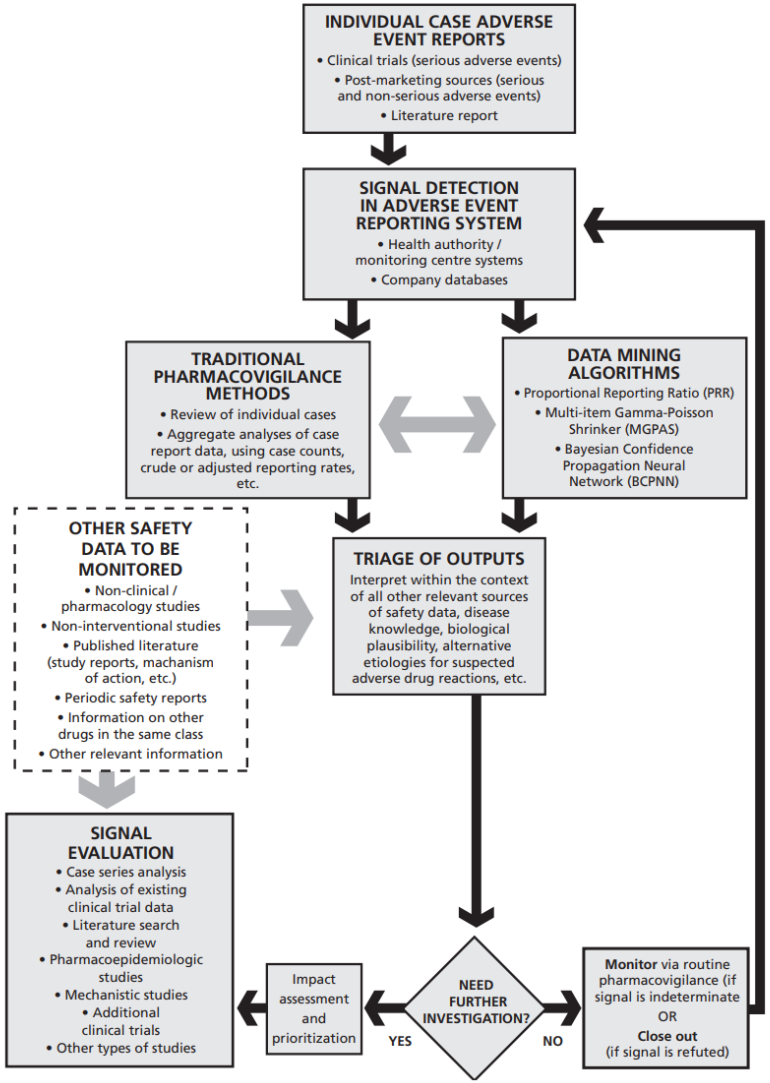
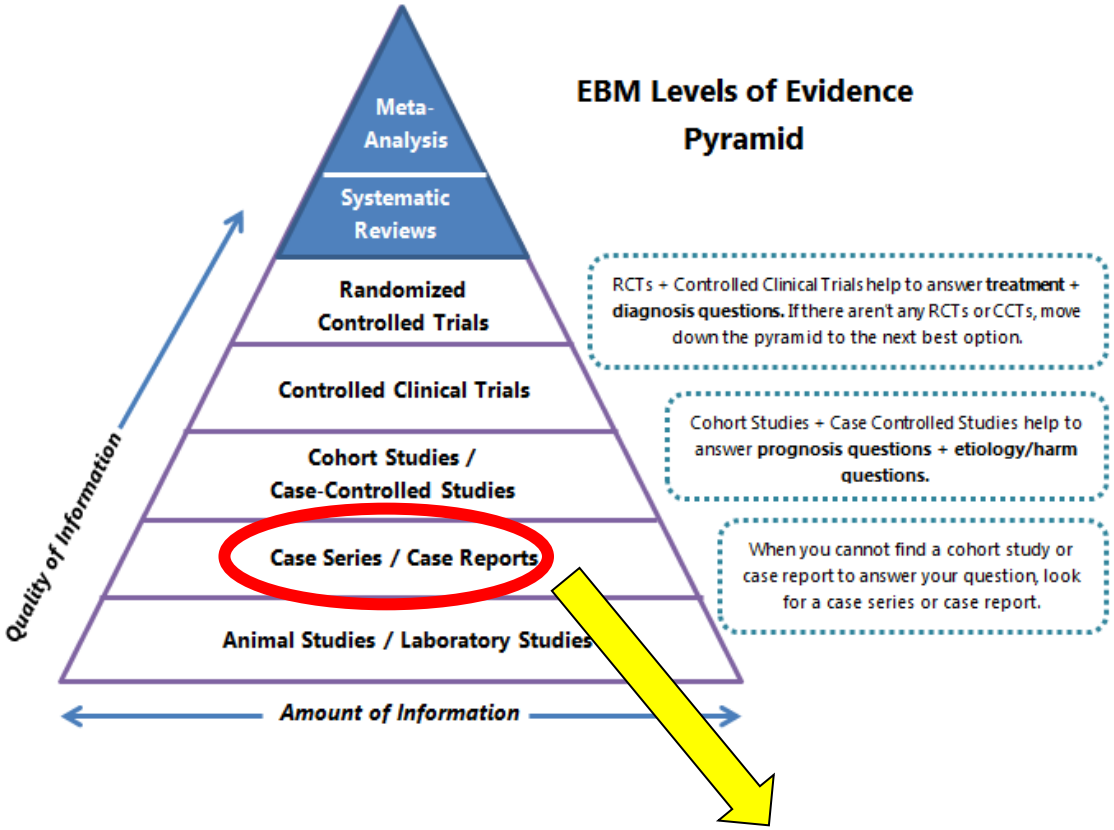
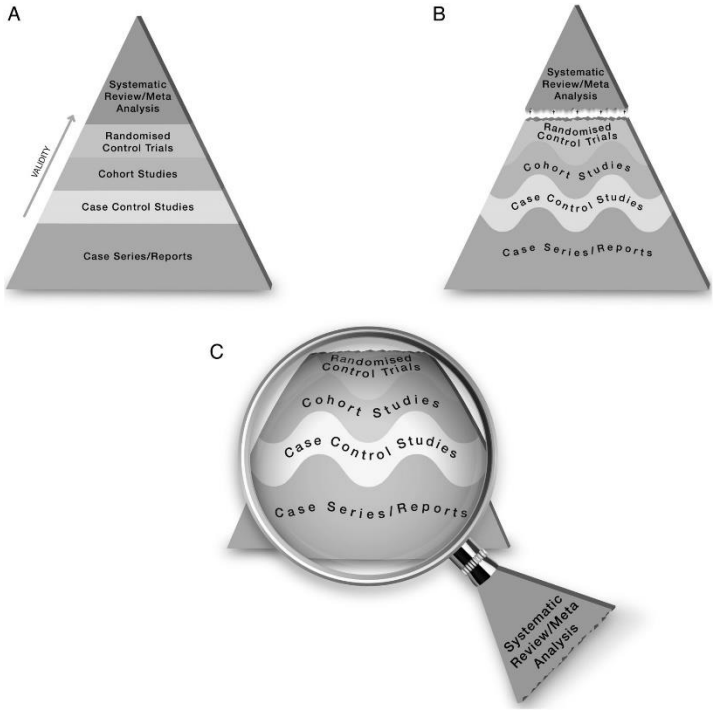


Figure 1. Signal management process



Evidence hierarchy





Need to look at the totality of data in evaluating possible signals and assessing risks

Risk Assessment

- In few instances, we can have confidence in causal association based on individual reports/clusters:
    - Injection site events
    - Short onset hypersensitivity
    - Isolation of vaccine virus (live) in body tissues
    - Event very similar to natural infection (live vaccines)
    - Cluster of onset times (if reporting bias excluded)
- But, majority of new events/signals will have unknown/ill-defined aetiology or occur naturally in population

→ **most new signals of serious risks require formal studies to assess causal association (Module 5)**

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016; **25**: 225–237
Published online 28 January 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3966

REVIEW

Near real-time vaccine safety surveillance using electronic health records—a systematic review of the application of statistical methods†

Andreia Leite[1]*, Nick J. Andrews[2] and Sara L. Thomas[1]

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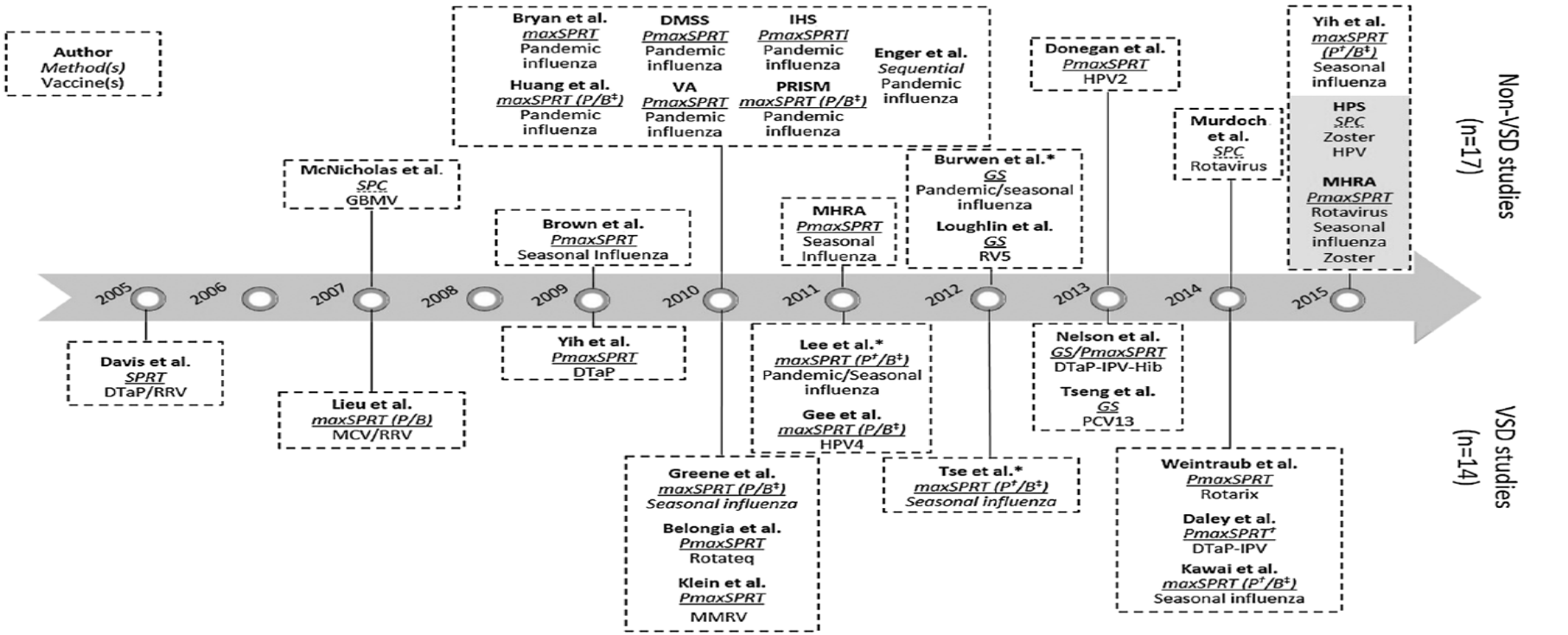
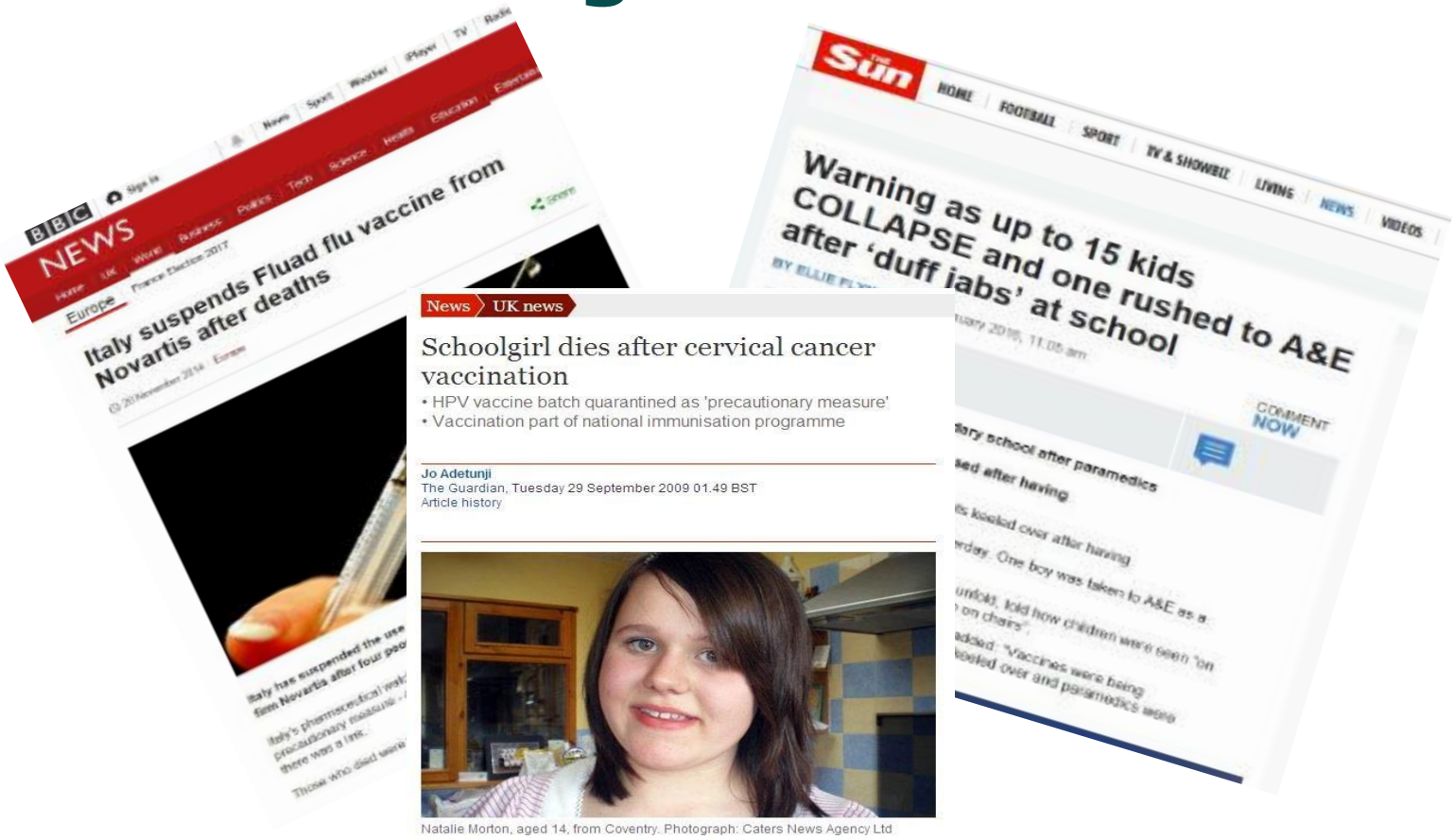
[2]*Statistics, Modelling and Economics Department, Public Health England, London, UK*

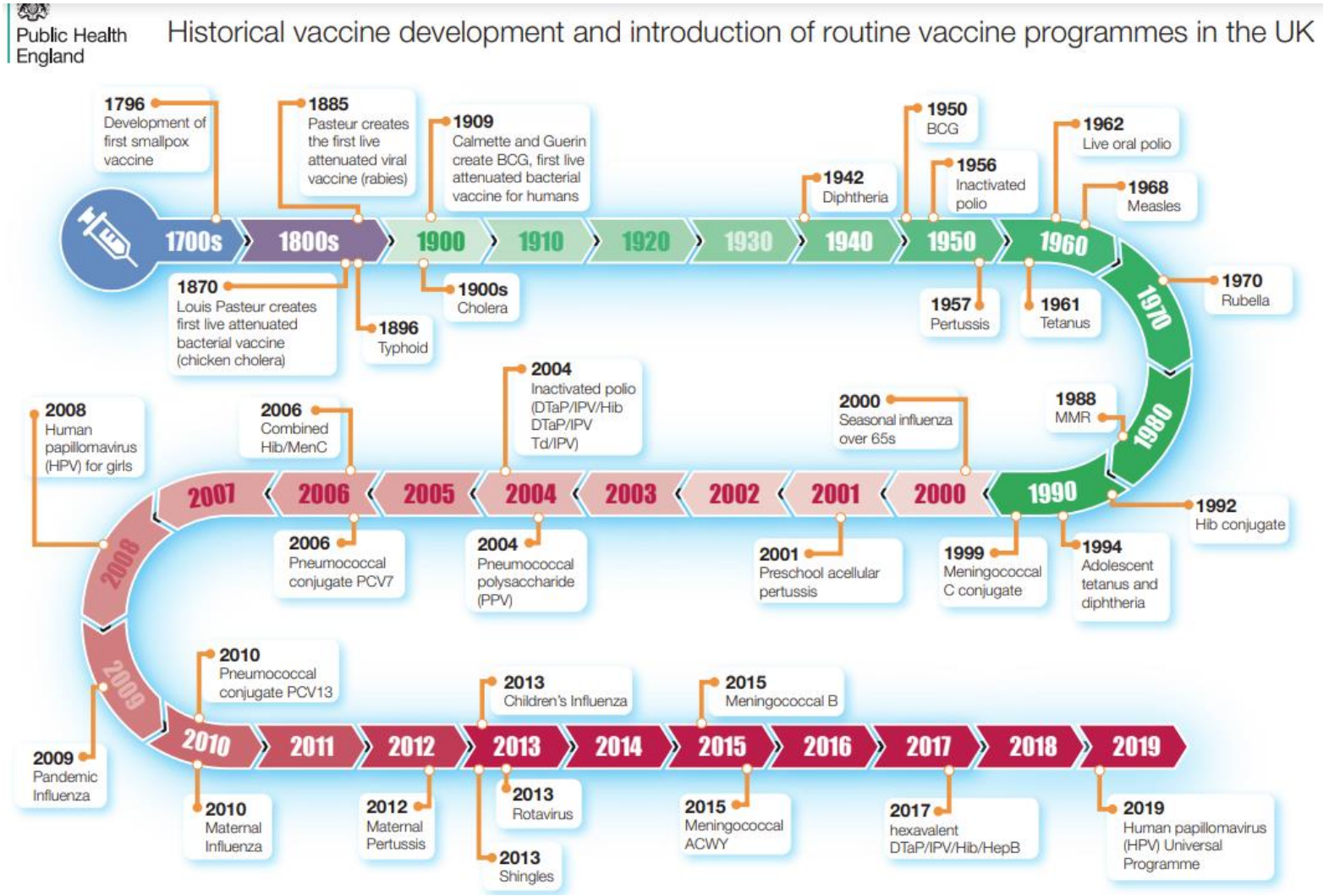


Incident management



- Signals and 'incidents' often arise outside of the usual ICSR reporting channels, and need managing very quickly – but principles of evidence-based evaluation still apply

Risk Management Planning



PhV planning

- Understand full safety specification (i.e. what we know prior to first authorisation)
    - Identify key risks and/or gaps
- Understand when and how programme will be implemented
    - Target Group
    - Immunisation schedule
    - Number in cohort – number of doses
    - Who will administer vaccine – primary care? schools?
- *Anticipate* and *plan* for the issues likely to arise
    - Look at the vaccine
    - Look at similar vaccines
    - Look at prior experience in similar populations

Pandemic 'swine flu' vaccines – 2009/10

- April 2009……

……October 2009

Thank you!

Muchas gracias !

Questions & Answers session (in Spanish)