Signal detection and assessment
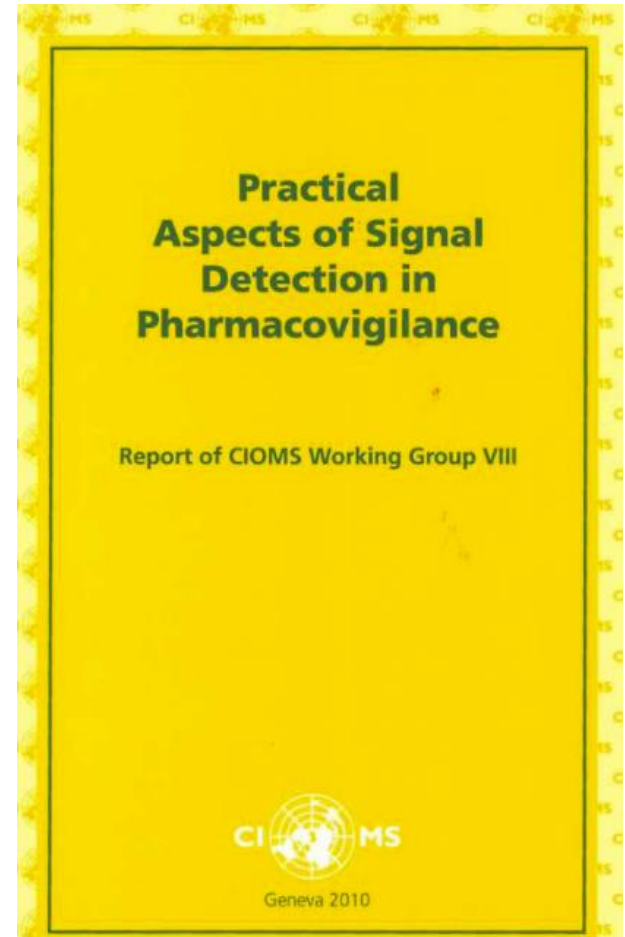
Module content

- Definition of a safety 'signal'
- Data sources for signal detection
- Evidence hierarchy
- Signal management process
- Signal detection methods – clinical; statistical
- Adverse events of special interest- AESIs
- AESI case definitions – Brighton Collaboration
- Signal detection tools
- Signal prioritisation
- Signal validation
- Causality assessment – 'can' it vs 'did' it

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'Signal' definition

- **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*" [CIOMS]

    - *i.e. a potential risk that requires further, initial analysis*

Practical Aspects of Signal Detection in Pharmacovigilance
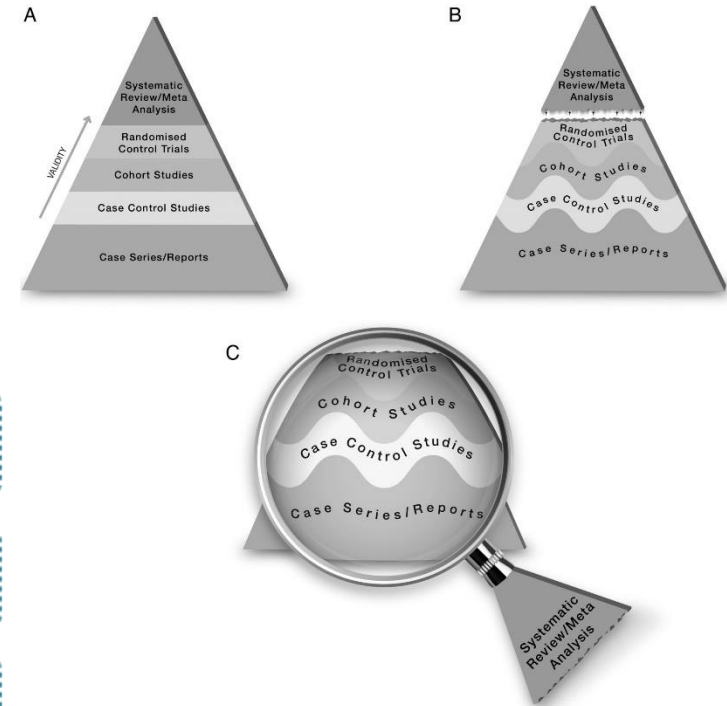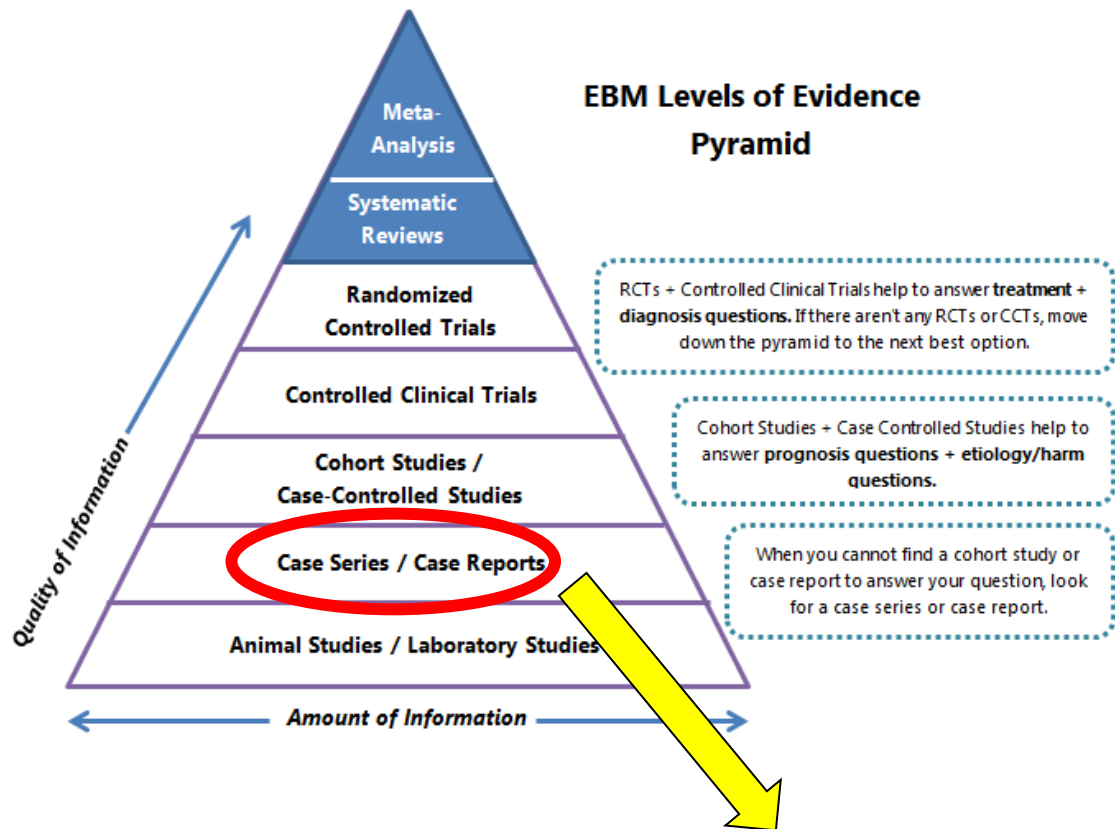
Report of CIOMS Working Group VIII

CI⦿MS

Geneva 2010

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

Signal data sources

- Signals can arise from (but not limited to):

  - Non-clinical and experimental data
    - Animal studies, in vitro, mechanistic studies

  - A single ICSR (AE/ADR/AEFI) report (a drug/vaccine-event combination)

  - A cluster/cumulative set of ICSRs (inc. aggregate/periodic safety reports)

  - Media/social media/public information

 - Clinical and epidemiological studies

Evidence hierarchy

EBM Levels of Evidence Pyramid

Pyramid levels (top to bottom): Meta-Analysis / Systematic Reviews; Randomized Controlled Trials; Controlled Clinical Trials; Cohort Studies / Case-Controlled Studies; Case Series / Case Reports; Animal Studies / Laboratory Studies

Quality of Information (vertical axis) — *Amount of Information* (horizontal axis)

RCTs + Controlled Clinical Trials help to answer **treatment + diagnosis questions.** If there aren't any RCTs or CCTs, move down the pyramid to the next best option.

Cohort Studies + Case Controlled Studies help to answer **prognosis questions + etiology/harm questions.**

When you cannot find a cohort study or case report to answer your question, look for a case series or case report.

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

5

Signal Management Process

- ## Signal detection
  - 'traditional' - quantitative

- ## Signal prioritisation
  - Urgent vs non-urgent

- ## Signal validation
  - Validated signal
    - Signal assessment/further analysis
      - Refuted signal (close signal)
      - Action required

  - Non-validated signal
    - 'false' signal (close signal)

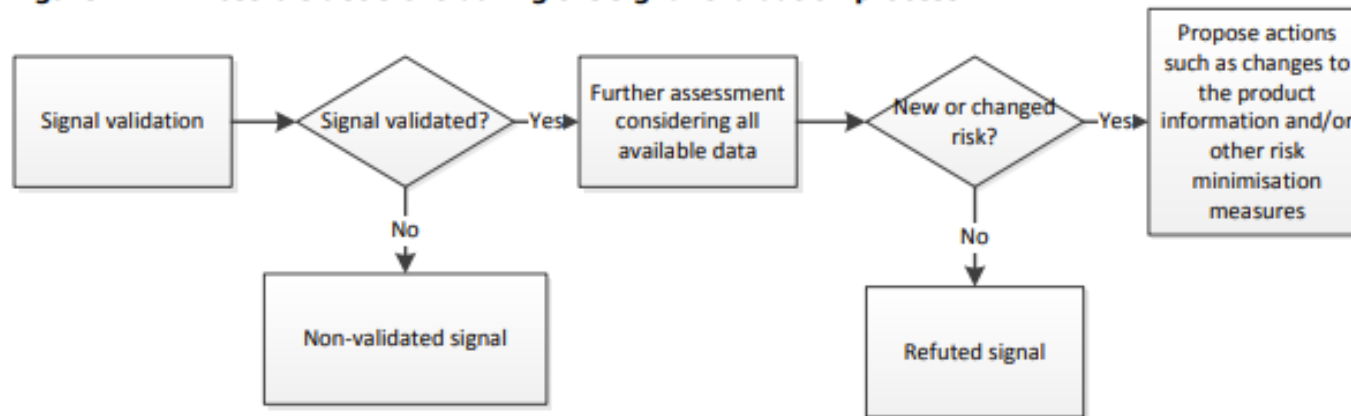 - **But, 'signals' are rarely truly closed and can always be re-opened as new data emerge**

Figure 1. Signal management process
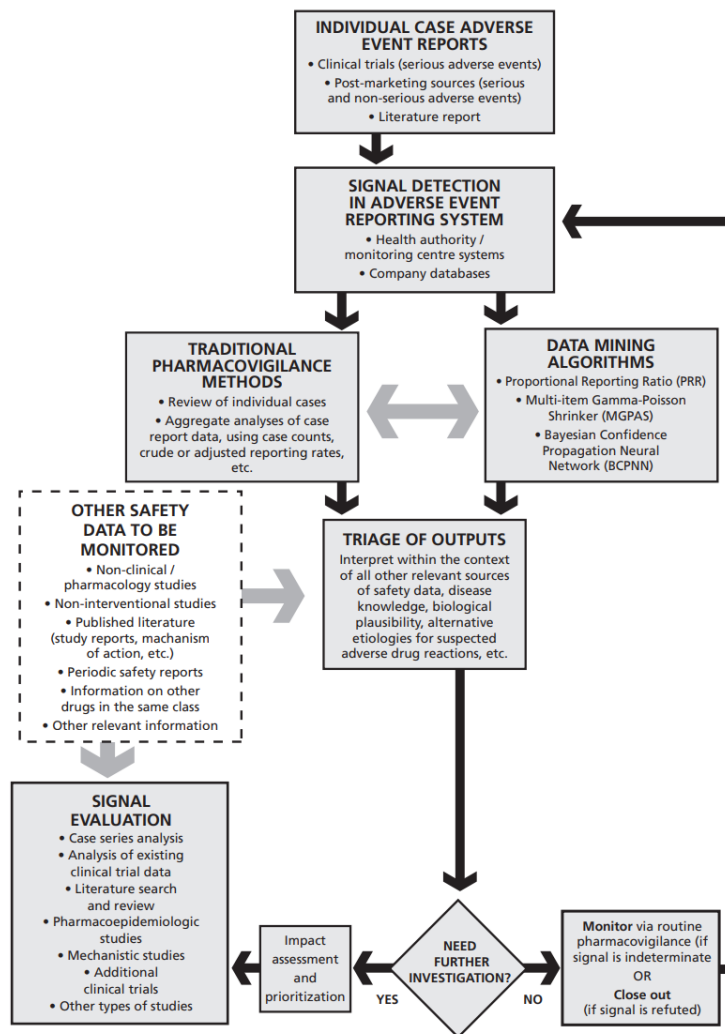
Source – CIOMS Working Group VIII

EU GVP Module IX

Figure IX.1 – Possible decisions during the signal evaluation process

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf

Source – CIOMS Working Group VIII

US FDA

FDA U.S. FOOD & DRUG ADMINISTRATION

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-pharmacovigilance-practices-and-pharmacoepidemiologic-assessment

Guidance for Industry

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2005
Clinical Medical

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Periodicity of signal detection

- Safety data collection and signal detection should be a continuous process
  - New risks can (in theory at least) emerge at any time point in a product life-cycle

- The frequency at which data are reviewed to detect signals depends on the level of accumulated knowledge

  - Well-established, generic compounds – at least every 6 months (EU GVP Module IX)

  - Novel compounds – more frequently
    - (MHRA guidance for COVID19 vaccines is at least weekly)

Signal Detection Methods

- Passive surveillance
  - Individual case/cluster/aggregate review (traditional)
  - Targeted review of pre-specified events (AESIs, DMEs)
  - Statistical analyses of PhV databases
    - Disproportionality analyses
    - Observed vs Expected analysis
    - Other methods

- Active surveillance
  - Dedicated surveillance programmes
  - Observed vs Expected analysis and data mining of secondary ('real world') data

- Social media monitoring
  - e.g. WEB-RADR

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Signal detection approaches

- 'Traditional' [qualitative] signal detection
  - Clinical evaluation of case/clusters/cumulative ICSRs
  - 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 can become very resource intensive

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

  - **<u>Both</u> should ideally be conducted in parallel**

Qualitative vs quantitative

- Statistical approach
  - Disproportionality

Study 1 – Which method to use?

Disp. measure	Implementation
PRR	$PRR_{025} \geq 1$ & $n \geq 3$ $PRR_{025} \geq 1$ & $n \geq 5$ $PRR \geq 3$ & $\chi^2 \geq 4$ & $n \geq 3$ $PRR \geq 2$ & $\chi^2 \geq 4$ & $n \geq 3$ $PRR \geq 2$ & $p <= 0.05$ & $n \geq 3$
ROR	$ROR_{025} \geq 1$ & $n \geq 3$ $ROR_{025} \geq 1$ & $n \geq 5$ $ROR_{025} > 1$ with shrinkage $ROR_{025} > 2$ & $n \geq 5$
IC	$IC_{025} > 0$
EBGM	EB05 ≥ 1.8 & $n \geq 3$ & EBGM ≥ 2.5 EB05 ≥ 1.8 **or** positive trend flag EB05 > 2.0 **or** positive trend flag
Urn	RR > 1 & unexpectedness $> 1 / 0.05$ RR > 1 & unexpectedness $> 500 / 0.05$

Source – PROTECT symposium - www.imi-protect.eu/documents/Session4.3_Statisticalsignaldetectionforspontaneousreports.pdf

- Clinical approach
  - The '*devil in the detail*'

Small databases

- Statistical analysis has less utility/validity in small databases
  - Smaller ICSR numbers, less diverse range of drug/vaccines

- Signal detection is more clinical and qualitative

Uppsala Monitoring Centre

SIGNAL DETECTION FOR NATIONAL PHARMACOVIGILANCE CENTRES WITH **SMALL DATA SETS**

The key steps for effective pharmacovigilance in settings with small data sets and limited resources are:

- flagging reports of interest as they come in
- searching local data for any similar reports
- searching VigiBase for anything similar
- assessing the strength of evidence for the link between drug and adverse effect
- communicating issues of concern to all relevant audiences or taking regulatory action and communication decisions

Uppsala Monitoring Centre

https://view.publitas.com/uppsala-monitoring-centre/signal-detection-for-national-pharmacovigilance-centres-with-small-data-sets

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Adverse events of special interest (AESI)

- An AESI is a pre-specified event that has the potential to be associated (whether causal or not) with a vaccine/drug and therefore warrants close vigilance and rapid signal detection (https://cioms.ch/wp-content/uploads/2017/01/Mgment_Safety_Info.pdf)

- They are not (usually) a regulatory requirement (i.e. in law) but are used in guidance to facilitate safety reporting/analysis in CTs and PhV planning in post-marketing

    - In clinical trials, AESIs allow for events that many not necessarily be serious (and therefore may not be notified) to be captured within the protocol (e.g. signs/symptoms non-serious diagnoses or laboratory findings that could be indicative of other serious events)

    - In post-marketing PhV, AESIs may additionally cover a range of events that do not qualify as product-specific 'potential/identified risks' [i.e. in the RMP] but that regulators or public health authorities request proactive vigilance of

- AESIs are sometimes based on general published guidance to achieve a harmonised approach to safety assessment - e.g. the *Priority List of COVID-19 Adverse events of special interest* developed by the Brighton Collaboration, funded by the Coalition for Epidemic Preparedness Innovations (CEPI) Safety Platform for Emergency vACcines (SPEAC) Project (https://brightoncollaboration.us/priority-list-aesi-covid/)

Designated Medical Events (DME)

- Certain events have, historically, been highly likely drug-induced (e.g. arrythmias, blood dyscrasias, bullous skin disorders)

- Some regulators (e.g. EMA) have developed lists of events that, irrespective of ICSR numbers/statistical signalling, deserve special attention in signal detection (a 'safety net')

- Similar concept to AESIs, not product-specific, intended as **guidance** to aid signal detection

- [not to be confused with EMA's 'Important Medical Events' list, which is intended to assist judgements on seriousness of individual ICSRs for expedited reporting]

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Case definitions I

- As the design of any safety study, a clear case definition and diagnostic certainty is crucial in PhV
    - In post-marketing, data of (very) variable quality collected across many countries
    - How else can we be sure are comparing like with like?

- A harmonised approach to use of SAE/ADR/AESI case definitions is strongly encouraged

- E.g. Brighton Collaboration (https://brightoncollaboration.us/)

Brighton Collaboration (BC)

- BC aims to enhance the science of vaccine research, by providing standardised, validated and objective methods for monitoring safety profiles and benefit to risk ratios of vaccines

- Case definitions for a range of common and serious vaccine-associated AEs published on BC website (e.g. fever, cellulitis, aseptic meningitis, narcolepsy)

- Case definitions usually divided into three levels of diagnostic certainty:
  - Level 1: definitive case
  - Level 2: probable case
  - Level 3: possible case
  - Level 4: insufficient to meet definition
  - Level 5: not a case

AESI Rationale to include as AESI (1, 2, 3, 4 and/or 5)	Brighton Case Definition Status
AESI included because they are seen with COVID-19 Disease [3,4]	
Acute respiratory distress syndrome	Submitted (Vaccine)
Multisystem inflammatory syndrome (children & adults)	Submitted (Vaccine)
Acute cardiovascular injury *(includes: myocarditis/pericarditis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia)*	Myocarditis/pericarditis near completion. Others not yet started
Coagulation disorder *(includes: thrombotic disorders, bleeding disorders)*	Thrombosis near completion; Bleeding disorder WG to be formed
Anosmia, ageusia	WG to be formed
Chilblain – like lesions	WG to be formed
Erythema multiforme	Not yet started
Single Organ Cutaneous Vasculitis	Published
Acute kidney injury	Published lab-based criteria (see *)
Acute liver injury	Published lab-based criteria (see #)
Acute pancreatitis NEW (Dec 2020)	Not yet started
Rhabdomyolysis NEW (Dec 2020)	Not yet started
Subacute thyroiditis NEW (Dec 2020)	Not yet started
AESI included because they have a proven or theoretical association with immunization in general	
Anaphylaxis [1,2]	Published
Thrombocytopenia [1,2,3,4]	Published
Generalized convulsion [1,2]	Published
Acute disseminated encephalomyelitis [4]	Published
Guillain Barré Syndrome [3,4]	Published
AESI included because they have a proven or theoretical association with specific vaccine platform(s)	
Acute aseptic arthritis r-VSV	Published
Aseptic meningitis Live vaccines	Published
Encephalitis / Encephalomyelitis Live vaccines	Published
Idiopathic Peripheral Facial Nerve Palsy Intranasal EColi Heat Labile Toxin Adjuvanted Vaccine	Published
Vaccine associated enhanced disease 1(Formalin inactivated measles/RSV; HIV), 2(Chimeric YF Dengue), 5 (SARS / MERS-CoVs)	In press (Vaccine)

[1] *Proven association with immunization encompassing several different vaccines*
[2] *Proven association with vaccine that could theoretically be true for novel COVID-19 vaccines*
[3] *Theoretical concern based on wild type disease immunopathogenesis*
[4] *Theoretical concern related to viral replication during wild type disease*
[5] *Theoretical concern because it has been demonstrated in an animal model with ≥ 1 vaccine platform*
* *Acute kidney injury – international consensus definition proposed by the Kidney Disease Improving Global Outcomes expert consensus group (www.kdigo.org)*
  - *Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours; OR*
  - *Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days OR*
  - *Urine volume ≤0.5 ml/ kg/ hour for 6 hours*
Acute liver injury – definition as used in majority of COVID-19 publications (but no international consensus):

https://brightoncollaboration.us/wp-content/uploads/2021/01/COVID-19-updated-AESI-list.pdf
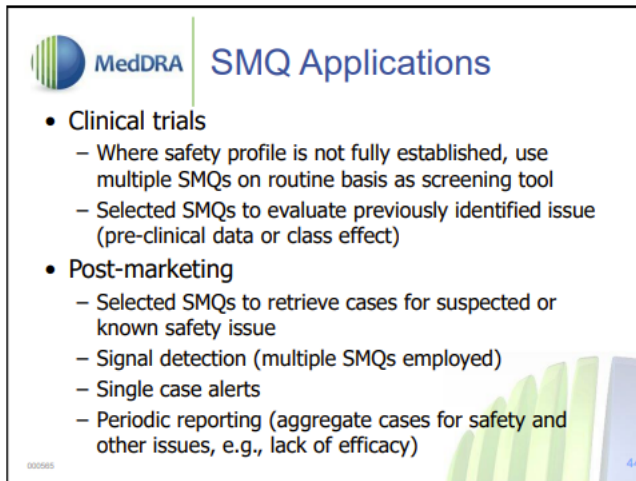
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Case definitions II

- When evaluating a signal it is good practice to consider/discuss the level of diagnostic certainty of cases wherever possible

  - If needed, stratify analysis by levels of diagnostic certainty

- However, post-marketing ICSRs often suffer from missing or poor quality information and level of diagnostic certainty not always clear

  - All ISCRs that report a particular event should be taken seriously and included in signal detection and analysis, even if level 4 or 5 (this includes non-medically validated consumer reports)

    - Signal detection and validation should always follow a conservative approach and have a low threshold

      - A 'weak' signal is still a signal
      - A more refined analysis can be undertaken following validation and as part of any formal/controlled study of a signal

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Event coding/retrieval

- Signal detection generally performed at MedDRA Preferred Term (PT) level

- But the same event can often be reported/coded in many different ways

- Important to look across related PTs (which may be across >1 SOC) when detecting and assessing signals include Investigations, Surgical SOC where relevant
  - and look at higher level groupings (HLT, HLGT, SOC) if relevant

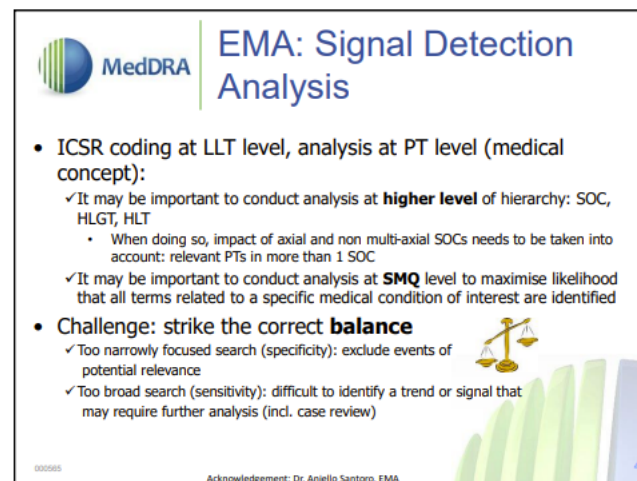- Use Standardised MedDRA Queries (SMQs) where relevant when assessing signals
  - (https://www.meddra.org/standardised-meddra-queries)

MedDRA SMQs

- Standardised MedDRA Queries (SMQs) are groupings of PTs from one or more MedDRA SOCs related to medical condition or area of interest

- Terms relate to signs/symptoms, diagnoses, syndromes, physical findings, laboratory and other test data, etc.

- Intended to aid in case identification

Disproportionality analysis (DPA) I

- Routine/regular screening of *larger* PhV databases to identify specific drug[vaccine]-event combinations (DEC) that occur more frequently than expected based on their individual frequency in the ICSR database

  - Confidence intervals or statistical significance tests are used to provide some protection against spurious associations

- A signal of disproportionality (SDR) is not necessarily a signal

  - SDRs are frequently 'false positives'

  - The next step is, generally, to review the case series (i.e. at a subjective, clinical level) to determine if a signal exists

Table 7: Contingency table used in disproportionality analysis

	Reports for event of interest	Reports for all other events	Total
Reports for drug of interest	A	B	A+B
Reports for all other drugs	C	D	C+D
Total	A+C	B+D	A+B+C+D

Source - https://cioms.ch/working_groups/working-group-viii/

Disproportionality analysis (DPA) II

- Several methods of DPA used in PhV databases exist, each of which is conceptually similar

PROTECT

Thresholds: example in WP 3.1

Statistics	Partner / Current Use	Implementations
Proportional Reporting Ratio PRR	EMA	PRR lower bound 95% c.i. ≥ 1 & n ≥ 3
	EMA	PRR lower bound 95% c.i. ≥ 1 & n ≥ 5
	MHRA (No)	PRR ≥ 3 & $\chi 2$ ≥ 4 & n ≥ 3
	Bayer	PRR ≥ 2 & $\chi 2$ ≥ 4 & n ≥ 3
	Roche	PRR ≥ 2 & p ($\chi 2$) <= 0.05 & n ≥ 3
Reporting Odds Ratio ROR	UMC	ROR with shrinkage, lower bound 95% c.i. > 1
	MEB	ROR lower bound 95% c.i. > 2 & n ≥ 5
	None	ROR lower bound 95% c.i. ≥ 1 & n ≥ 3
	None	ROR lower bound 95% c.i. ≥ 1 & n ≥ 5
Information Component IC	UMC	IC lower bound 95% confidence interval (c.i.) > 0
Empirical Bayes Geometric Mean EBGM	MHRA	EB05 ≥ 1.8 & n ≥ 3 & EBGM ≥ 2.5
	AZ	EB05 ≥ 1.8 or positive trend flag
	GSK	EB05 > 2.0 or positive trend flag
URN model	None	Reporting Ratio > 1 & unexpectedness > 1 / 0.05
	None	Reporting Ratio > 1 & unexpectedness > 500 / 0.05

Signal Detection Tools I

- Depending on the size of an organization and nature/quantity of the ICSR database and products for which they are responsible, a range of tools are in use from simple, manual processes to purpose-built software

  - 'Smaller' organisations – e.g. 62% of LMIC vaccine manufacturers (who may still supply large quantities of vaccine) still record ICSRs via a paper-based or excel system, and only 29% use an electronic system for signal detection (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7311355/?report=reader)

  - Uppsala Monitoring Centre – Vigilyze system (https://who-umc.org/pv-products/vigilyze/)

  - EMA – EVDAS (https://www.ema.europa.eu/en/documents/presentation/presentation-eudravigilance-data-analysis-system-evdas-training-national-competent-authorities_en.pdf)

Signal detection tools II

- Proprietary software –
  - E.g. Oracle Empirica Signal (used by e.g. MHRA, FDA, industry…)

Source – Oracle - www.oracle.com/a/ocom/docs/industries/health-sciences/empirica-signal-ds.pdf

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Observed vs Expected (O/E)

- All of the aforementioned signal detection approaches rely on analysis of ICSRs alone (i.e. the numerator)

- By supplementing ICSR data with measures of vaccine exposure (a denominator) and expected 'background' rates of events an additional form of DPA can be applied – 'observed vs expected' analysis

- O/E can be a very useful routine or *ad hoc* signal detection method, and can also be used in validation and refinement of signals

COMMENTARY

Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines[†]

Olivia Mahaux*, Vincent Bauchau and Lionel Van Holle

Vaccine Clinical Safety and Pharmacovigilance, GSK Vaccines, Wavre, Belgium

O/E principles I

- Pre-define AESIs
- Establish a baseline 'expected'
  - i.e. how many cases of X might we expect to occur within Y weeks for every Z thousand people vaccinated
  - Ideally stratify by age, gender, region
    - Use available literature or analysis of electronic healthcare data from a time period recently before vaccination
- Obtain as near real-time information as possible on vaccine exposure
  - Ideally, actual doses administered in the region, stratified by age, gender, or a reasonable estimate (sales/supply data)
- On a continuous basis, compare real-time ICSR reporting rates of AESIs ('observed') to the expected incidence

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O/E principles II

- As this is based on passive surveillance, there will be under-reporting
  - Adjust ICSR numbers for assumed levels of under-reporting (this can only be a guestimate)

- As continuous, multiple analysis can yield chance clusters, apply sequential statistical analysis
  - E.g. Maximised Sequential Probability Ratio Test (MaxSPRT)

- Determine a signal 'threshold' (i.e. the point at which O exceeds E)
  - Generate signals for further validation

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O/E example

Maximised SPRT for Guillain-Barre Syndrome for patients aged < 65 years (2009–2010)
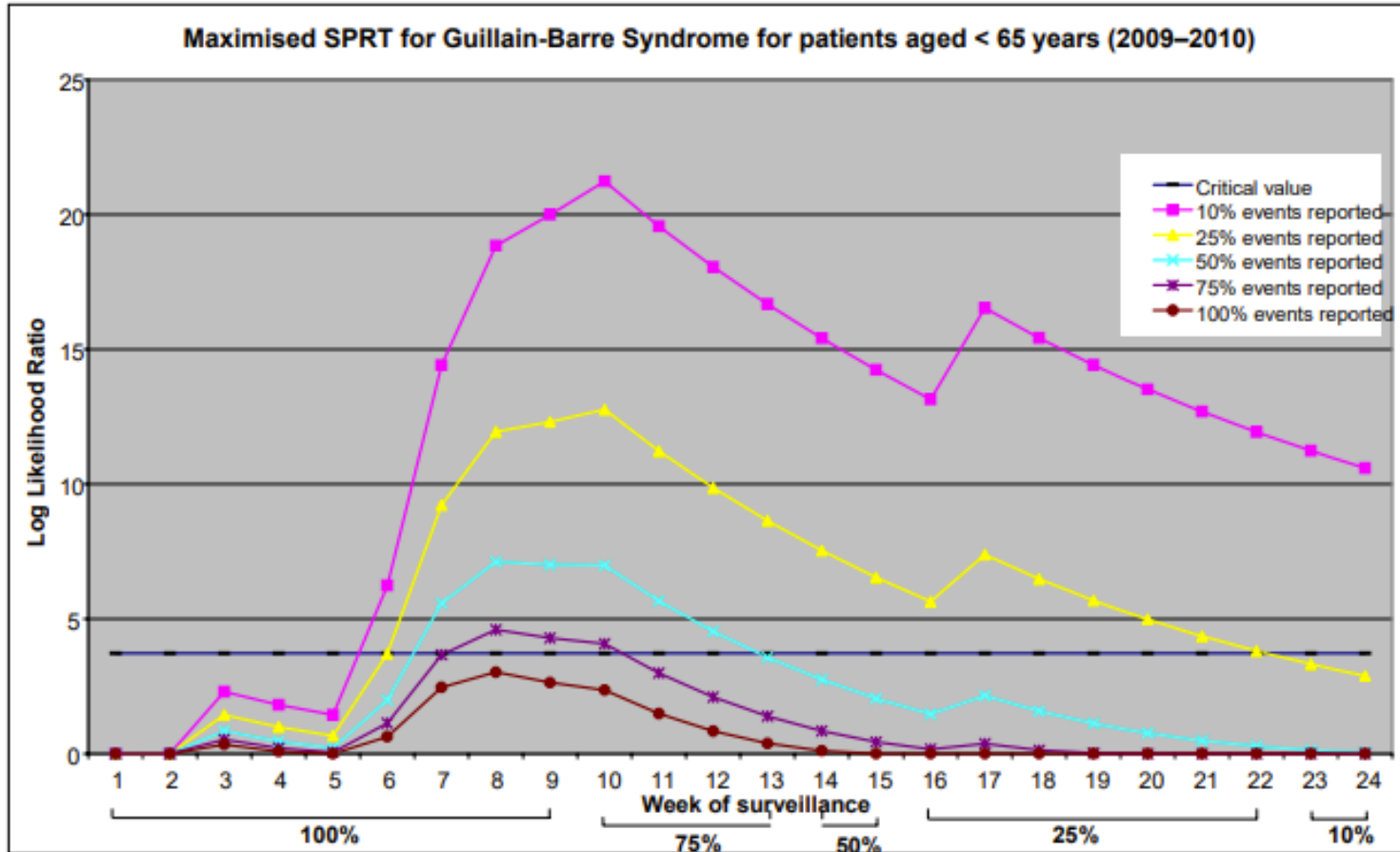
UK MHRA analysis of GBS following 2009 swine flu vaccine

Reveals a marginal safety signal 6 weeks into immunisation programme

O/E principles III

- Strengths
  - uses existing, real-time/available data sources
  - cheap, rapid, flexible, adaptable
  - can identify rare risks
  - allows ICSR reports to be placed in context
  - Can respond rapidly

- Limitations
  - under-reporting if AESIs
  - delayed reporting (e.g. narcolepsy issue)
  - requires prior hypothesis (AESIs)
  - cannot confirm causality
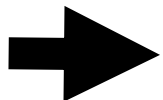
But is a rapid, evidence-based risk assessment to inform decision-making and signal prioritisation, pending any formal observational studies

Subsequent UK study

Table 1

Relative incidence (RI) estimates with 95% confidence intervals from the SCCS analyses with a 42 day week risk window after vaccination.

Model	RI (95% CI[a])	Cases in risk period
Base[b]	1.05 (0.37–2.24)	9
No period effect	1.26 (0.48–2.66)	9
End of follow-up April 10	1.15 (0.45–2.49)	9
Onset date set to date of hospitalisation – 7 days if onset unknown	1.03 (0.38–2.26)	9
Only include cases where onset to admission <10 days	1.25 (0.27–3.78)	6
Unknown pandemic vaccine date case in risk period	1.17 (0.43–2.60)	10
Unknown pandemic vaccine date outside risk period	1.01 (0.36–2.21)	9
Seasonal vaccine risk period included, unknown seasonal status cases dropped	0.77 (0.26–1.82) [pan]	7
	1.23 (0.57–2.14) [seas]	16
Seasonal vaccine risk period included, unknown seasonal status cases counted included as unvaccinated.	1.02 (0.36–2.19) [pan]	9
	1.20 (0.63–2.07) [seas]	16
Vaccinated cases only method	0.89 (0.23–3.43)	9
Standard method with no pre-vaccination low period	1.42 (0.65–3.08)	9
Standard method with 28 day pre-vaccination low period	1.33 (0.60–2.91)	9
Standard method with 90 day pre-vaccination low period	1.08 (0.48–2.40)	9

[a] 95% CI's calculated using percentile bootstrap method for pseudo-likelihood analysis or normal method for standard and vaccinated cases only analyses.
[b] Pseudo-likelihood method with a monthly period effect, follow up to May 2010, unknown date of vaccination case dropped.

https://doi.org/10.1016/j.vaccine.2011.08.069

- Active UK-wide case ascertainment

  - 9 GBS cases within 6 weeks of vaccination (vs 10 ICSR reports)

  - Some reassurance that 'real-time' surveillance was effective – signal invalid

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Other DPA methods and further reading.....

Vaccine 37 (2019) 49–55

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

ELSEVIER

Tree-based scan statistic – Application in manufacturing-related safety signal detection

Olivia Mahaux*, Vincent Bauchau, Ziad Zeinoun, Lionel Van Holle
Vaccine Clinical Safety and Pharmacovigilance, GSK, Waver, Belgium

> Drug Saf. 2005;28(10):835-42. doi: 10.2165/00002018-200528100-00001.

Data mining in pharmacovigilance: the need for a balanced perspective

Manfred Hauben [1], Vaishali Patadia, Charles Gerrits, Louisa Walsh, Lester Reich

Affiliations + expand

Leveraging the Variability of Pharmacovigilance Disproportionality Analyses to Improve Signal Detection Performances

Charles Khouri [1,2,3]*, Thuy Nguyen [1], Bruno Revol [1,2,3], Marion Lepelley [1,2], Antoine Pariente [4,5], Matthieu Roustit [2,3] and Jean-Luc Cracowski [1,3]

ORIGINAL REPORT

Signal detection on spontaneous reports of adverse events following immunisation: a comparison of the performance of a disproportionality-based algorithm and a time-to-onset-based algorithm

Lionel Van Holle* and Vincent Bauchau

Research Group (VSRG), Vaccines Clinical Safety & Pharmacovigilance (VCSP), GlaxoSmithKline Vaccines,

> Drug Saf. 2016 Jun;39(6):469-90. doi: 10.1007/s40264-016-0405-1.

Good Signal Detection Practices: Evidence from IMI PROTECT

Antoni F Z Wisniewski [1], Andrew Bate [2], Cedric Bousquet [3] [4], Andreas Brueckner [5], Gianmario Candore [6], Kristina Juhlin [7], Miguel A Macia-Martinez [8], Katrin Manlik [9], Naashika Quarcoo [10], Suzie Seabroke [11], Jim Slattery [6], Harry Southworth [12], Bharat Thakrar [13], Phil Tregunno [11], Lionel Van Holle [14], Michael Kayser [15], G Niklas Norén [7]

Active surveillance

- Aside from analysis of ICSR data/databases routine and/or *ad hoc* systems can be put in place, which do not rely on passive reporting of ADRs but which actively follow-up defined cohorts of vaccinees

- These approaches tend to be more resource-intensive and smaller than population-wide surveillance, and more suited to detection or characterisation of less rare risks

Yellow Card | Vaccine Monitor

v-safe℠
after vaccination
health checker

NEW! | People who have already been vaccinated can enter an additio[n]
Parents or guardians can enroll their vaccinated children.

ow Card Vaccine Monitor

is monitoring suspected side effects to COVID-19 vaccines. Please register before
your vaccination by clicking 'Sign in or register'. If you have already received your
u can still sign up.

IMPACT

Canadian Immunization Monitoring Program, ACTive
Programme canadien de surveillance active de l'immunisation

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Using 'Real world' data

- In this context 'real world' data refers to routinely collected, secondary healthcare records (and usually electronic healthcare records and medical insurance databases)

- In PhV, such datasets are generally used to undertaken pharmepi studies of possible signals, but can also be used in signal detection (provided the same data are not used to generate and test a hypothesis)

- A similar approach to O/E analysis of ICSRs can be undertaken, which removes the reliance on passive reporting and uses the medical records as the AESI numerator

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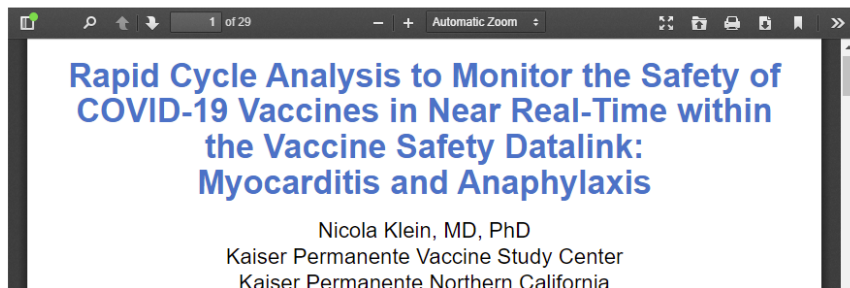
Rapid Cycle Analysis (RCA)

- RCA is a form of O/E developed by the US CDC using the Vaccine Safety Datalink (VSD)

Rapid cycle analysis to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink : Myocarditis and anaphylaxis

August 30, 2021

By Klein, Nicola P.

Series: ACIP meeting COVID-19 Vaccines

Rapid Cycle Analysis to Monitor the Safety of COVID-19 Vaccines in Near Real-Time within the Vaccine Safety Datalink: Myocarditis and Anaphylaxis

Nicola Klein, MD, PhD
Kaiser Permanente Vaccine Study Center
Kaiser Permanente Northern California

Vaccine
Volume 32, Issue 42, 22 September 2014, Pages 5390-5398

Review

The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety

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https://stacks.cdc.gov/view/cdc/109493

*Also see US FDA's PRISM programme -
https://pubmed.ncbi.nlm.nih.gov/24331080/

Further reading......

REVIEW

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

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SPECIAL ARTICLE

Good Signal Detection Practices: Evidence from IMI PROTECT

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Gianmario Candore[6] · Kristina Juhlin[7] · Miguel A. Macia-Martinez[8] ·
Katrin Manlik[9] · Naashika Quarcoo[10] · Suzie Seabroke[11] · Jim Slattery[6] ·
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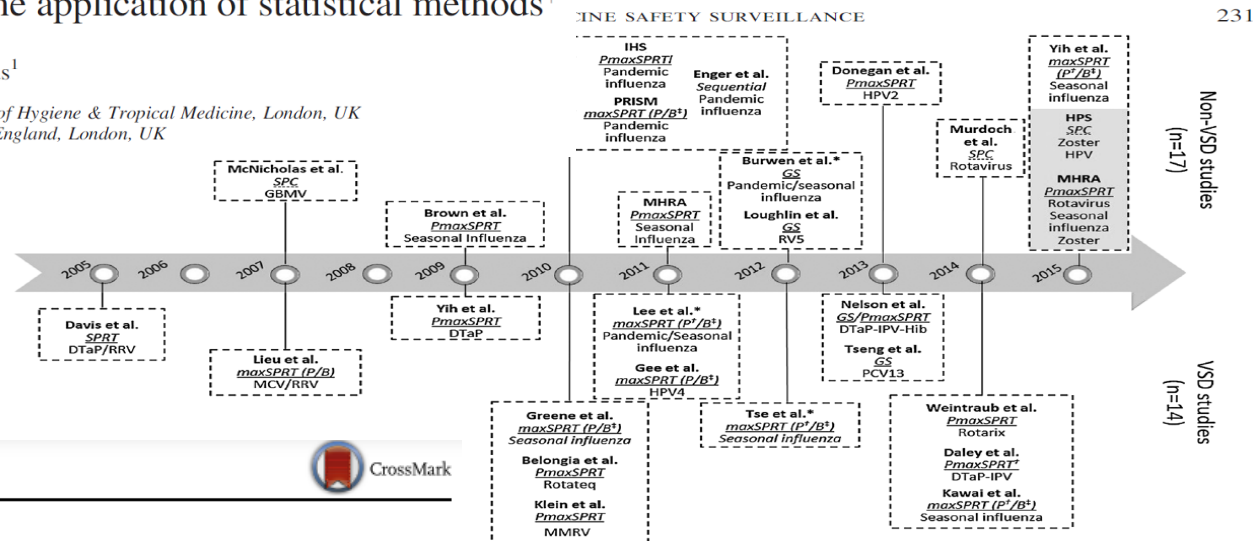
Social Media Monitoring

- In addition to surveillance of traditional PhV data sources, the value of surveillance of social media messaging and other 'big data' sources for signal detection is being actively explored

WEB-RADR

WEB-RADR: Recognising Adverse Drug Reactions

Working together to improve pharmacovigilance through new technology

https://web-radr.eu/

Social media and pharmacovigilance: A review of the opportunities and challenges

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Signal prioritization I

- PhV systems can generate large numbers of signals so how do we decide where to focus resource?

- The following are points to consider (from EU GVP IX):

  - severity, seriousness, outcome, reversibility, preventability of the ADR
  - patient exposure and the estimated frequency of the ADR
  - the consequences of treatment discontinuation on the disease under treatment and the availability of other therapeutic options (not relevant to vaccines)
  - the expected extent of the regulatory intervention (e.g. addition of adverse reactions, warnings, contraindications, additional risk minimisation measures, suspension, revocation)
  - whether the signal is likely to apply to other substances of the same class of medicinal products

- **And, in some circumstances, signals that could cause media attention and/or public concerns (e.g. adverse events following mass immunisation) may deserve special attention**

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Signal prioritisation II

- Signal prioritization is a largely subjective exercise but evidence-based and weighted methods can be applied
    - e.g. UK MHRA's - Regulatory Pharmacovigilance Prioritisation System (RPPS)

- RPPS - A priority score is assigned based on weighted measures of potential public health implications, MHRA legal obligations, the strength of evidence for a causal effect, and public perceptions

SCOPE Work Package 5
Signal Management – Best Practice Guide

SCOPE

A novel tool for prioritising pharmacovigilance issues within the MHRA was developed and implemented, called the Regulatory Pharmacovigilance Prioritisation System (RPPS). The RPPS tool (see Annex 5) provides a systematic approach to prioritise signals according to four categories: health consequences, strength of evidence, regulatory obligations and public perception.

Other tools are described in the literature, such as the 2012 FDA (32) publication of a guidance for Classifying Significant Post-marketing Drug Safety Issues. Another prioritisation tool was developed and tested in a MAH database by Levitan et al (33).

https://www.ema.europa.eu/en/documents/other/scope-training-signal-management-best-practice-guide_en.pdf

Original Research Article | Published: 03 July 2013

Development of a Novel Regulatory Pharmacovigilance Prioritisation System: An Evaluation of Its Performance at the UK Medicines and Healthcare products Regulatory Agency

Suzie Seabroke ✉, Lesley Wise & Patrick Waller

Drug Safety **36**, 1025–1032 (2013) | Cite this article

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Signal prioritisation III

- Example- MHRA – RPPS Categorisation

PUBLIC HEALTH	Points		AGENCY OBLIGATIONS	Points
>= 100,000 USERS/POTENTIAL HIGH USAGE	3		MINISTERIAL CONCERN	1
> 1 IN 1000 AFFECTED	2		PARLIAMENTARY QUESTIONS	1
IA HEALTH CONSEQUENCES > 0.6	4		UK RAPPORTEUR OR RMS	3
AT LEAST 20 CASES OR 3 FATALITIES (SR)	1		MA HOLDER APPLIED	2
STRENGTH OF EVIDENCE			PUBLIC PERCEPTION	
EBGM>10 OR RR>3	2		RECENT MEDIA ATTENTION	3
MORE THAN 1 DATA SOURCE	4		AT LEAST TWO FRIGHT FACTORS	4
HIGH LEVEL EVIDENCE	4		HARMFUL MISPERCEPTIONS	1
BIOLOGICAL PLAUSIBILITY	2		OTHER INDICATION FROM PUBLIC	3

- The target for issues in the top category is 3 months, for those in the increased category the target is 6 months and for those in the standard category the target is 12 months.

Signal validation

- The next 'step' after signal detection (and prioritisation, if done) is to 'validate' the signal and to determine what, if any, further analysis is required

- This may involve a more detailed analysis of the ICSR cases that generated the signal (e.g. if the signal was purely statistical), or may involve using additional, available data to determine the strength of the signal (which can in turn help to further prioritise a signal) and to refine it (e.g. to a more specific event or risk group)

- Although 'validation' is defined as a particular step in EU regulatory terms (GVP IX), on a *scientific level* the evaluation of a signal is a continuous process that <u>should not be constrained by specific 'steps' or regulatory terminology</u>

  - **What we are essentially trying to do is determine whether the evidence available to us is sufficient to suggest a causal association and whether action should be taken**

Causality assessment

- 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
    - 'It can' does not necessarily mean 'it did' in any individual case, particularly for events that can occur naturally

- 'It did' does not always mean 'it can' (i.e. for previously unrecognized ADRs)
    - Very few examples when individual cases have proven causality (see next slide)
    - These individual judgments are mostly based on subjective clinical opinion, used to decide clinical management of individual patients, or to determine reportability of a case
    - in most cases, individual-level causality judgements are just a part of the total evidence base and the signal detection process

- If our role is to monitor the safety of a product and make decisions on its benefit-risk balance and risk minimization, then are focus is on the 'can it' and the totality of evidence

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Individual causality I

Management of Safety Information from Clinical Trials

### Report of CIOMS Working Group VI

(2) Causality Assessment

Investigators must inform the sponsor of serious adverse events as soon as they become aware of them and, by using clinical judgement, should assess the potential link to the drug treatment. Some hold the opinion that causality determinations on individual case reports are a "waste of time" especially for randomised studies. However, while individual case causality assessment may be difficult for both investigators and sponsors, the investigator's opinion contributes to the sponsor's decision on the necessity for expedited reporting to health authorities – a requirement that depends on individual case attribution. Causality judgments based on analysis of multiple cases/aggregate data are almost always more meaningful and typically have a greater impact on the conduct of clinical trials, including changes to informed consent documents, study design, and core safety information.

https://cioms.ch/wp-content/uploads/2017/01/Mgment_Safety_Info.pdf

Causality assessment of an adverse event following immunization (AEFI)

User manual for the revised WHO classification

Second edition
2019 update
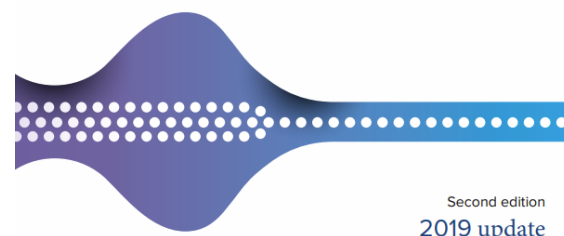
2. The individual level

At the individual level it is usually not possible to establish a definite causal relationship between a particular AEFI and a particular vaccine on the basis of a single AEFI case report. However, it is important to try assessing this relationship in order to identify a possible new vaccine product-related reaction, as well as to determine if the event is preventable or remedial – such as a product-related quality defect or immunization error.

https://www.who.int/publications/i/item/causality-assessment-aefi-user-manual-2019

Individual causality II

- In very few instances can we have confidence in causal association based on individual reports/small clusters, e.g.:

  - Injection site events
  - Short onset hypersensitivity (excluding other allergens)
  - Isolation of vaccine virus (live) in body tissues (or other biomarkers linked to the vaccine)
  - Event very similar to natural infection (live vaccines)
  - Events that don't occur naturally (or occur very rarely), e.g. TTS
  - Consistent rechallenge

- In such cases, more weight can be placed on the individual-case causality assessment in respect of the 'can it' question, and therefore whether (regulatory) action is required

- However, the majority of new events/signals will have unknown/ill-defined aetiology or will occur naturally in population, and individual case judgements will carry less weight

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Causality assessment

- In most cases, a well-designed pharmacoepidemiology study is needed to properly evaluate, confirm and quantify a safety signal, particularly if the event can also occur naturally in the patient population (pharmepi studies are a subject of the next module)

- But studies take time and may not always provide a clear conclusion
  - it is often the case that decisions need to made in the absence/in advance of such studies and based on ICSR reports and other available data

- So how do we assess the strength of a signal and causality based on case reports/available data?

Key questions to consider

- Does the event occur naturally in target population, and how frequently?

- If >1 case, is there a consistent clinical pattern that could be suggestive of causality (noting any bias towards likelihood of voluntary reporting events that fit a more 'plausible' risk window)?

- What is a plausible risk window? Is onset time plausibly related to vaccine based on the pathophysiology relative to the vaccine immunology?

- Are there any specific/unique/unusual clinical or lab findings that could indicate vaccine effect?

- Is there obvious confounding/risk factors that provide an alternative aetiology (noting that this is informative to signal strength, but should not necessarily be a rationale to dismiss a signal if O/E or other factors are suggestive of signal)

- Is there known/potential biological plausibility based on the vaccine construct/immunology or association with related vaccines/vectors/adjuvants, inc. any non-clinical data (noting that a lack of biological plausibility is **not** a rationale to dismiss a signal)?

- Are case numbers more cases than expected based on exposed person-time and O/E, taking account of any uncertainty around case ascertainment (e.g. active FU vs under-reporting via passive surveillance)

- Is there any proven/disproven associations with similar vaccines?

  - **Based on all of above, what is the strength of evidence, is it a signal, what further analysis is needed?**
    - **Or is there sufficient evidence now to determine likelihood of a causal association?**

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Bradford Hill criteria

Meeting January 14 1965

President's Address

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS (*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby

observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the un-

9 principles for causation

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient

6. Biological plausibility
7. Coherence
8. Experiment
9. Analogy

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Bradford Hill criteria

- Strength (the size of the effect, often refers to the statistical association) – larger effect may be more likely causal, but small effect does not mean non-causal
- Consistency (reproducibility) – same effect seen elsewhere (other populations, data sources, similar clinical pattern)
- Specificity – how uniqueness it is
- Temporality – risk window, time to onset (but TTO often biased)
- Biological gradient – dose-response effect
- Biological plausibility – pathophysiology, mechanism of action
- Coherence – similar to plausibility – do the pieces fit together?
- Experiment – e.g. re/dechallenge
- Analogy – causal association with similar products

  - Can be applied to multiple data sources, guiding principles only, not all criteria need to be met

- This is still a largely *subjective* evaluation of the evidence

Many other methods.......

Review Article

AN OVERVIEW OF VARIOUS SCALES USED IN CAUSALITY ASSESSMENT OF ADVERSE DRUG REACTIONS

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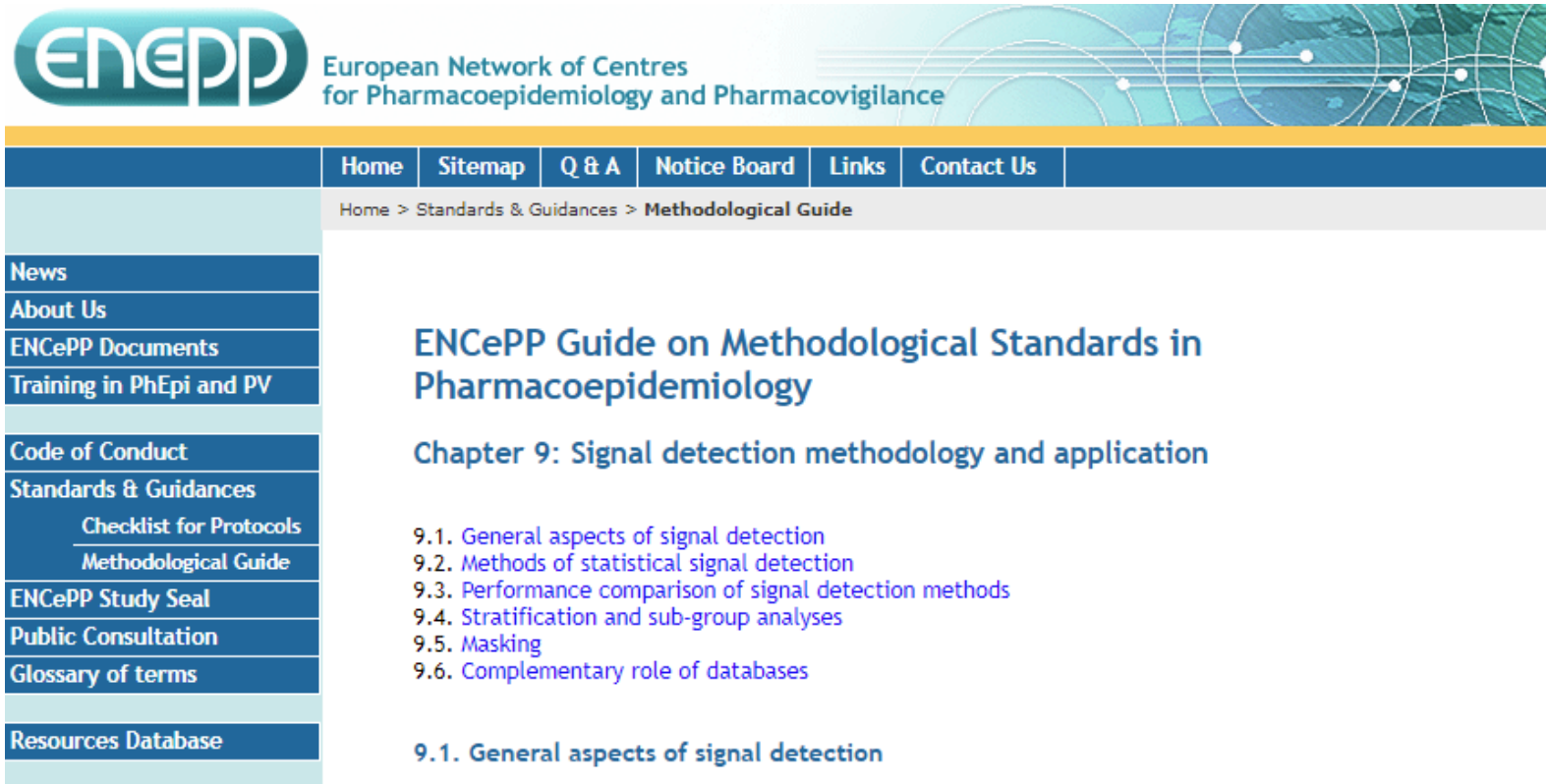
ABSTRACT

Establishing a relationship of causality between the medications received and the events occurred utilizing causality assessment scale is much needed to reduce the occurrence of Adverse Drug Reactions (ADRs) and to prevent exposure of patients towards additional drug hazards. Causality assessment can be defined as the determination of chance, whether a selected intervention is the root cause of the adverse event observed. The causality assessment is the responsibility of either a single expert or an established committee. As it is a common phenomenon of variable perception of knowledge and experience by each expert, there is a high possibility of disagreement and inter-individual variability on assessment. Many of the causality assessment methods have their advantages and disadvantages. However, no single scale has been adopted as standardized and considered for uniform acceptance.

- Lots of methods and papers published over the years
- No method is perfect or will give the 'right' answer

  - Need to balance relative strengths and weaknesses of evidence, consider totality of data, consult experts, ***and keep an open mind***!

Further reading…..

https://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

Thank you!

Muchas gracias !

Questions & Answers session (in Spanish)