Vaccine Safety Monitoring

Part 1: How does it work now?

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CARM

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH
www.medsafe.govt.nz

Outline

- Components
- Current Process
- Future activities

Components of a vaccine vigilance system

The Medicines Act 1981	Immunisation programme	We can always use more
Yes – keep listening	Official Information Act	WHO

Vaccine Safety

- Intrinsic safety
  - Compare yellow fever vaccine with influenza
- User-dependent safety
  - Avoid live vaccines in immunosuppressed
- Population vs Individual
  - Regulator concerned with population as a whole, health professionals need to care for individual

Vigilance Process

What is a Signal?

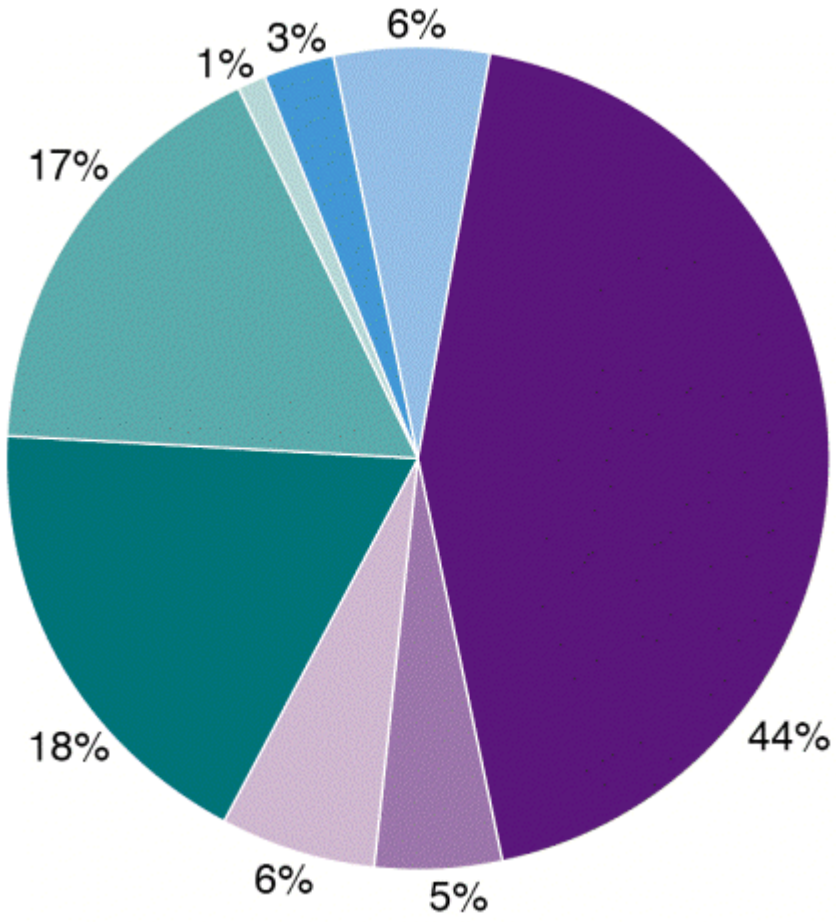
WHO Definition :

‘reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously….’

Sources of Signals

- Spontaneous reporting schemes
  - Centre for Adverse Reactions Monitoring (CARM)
  - WHO, sponsors
- Data from formal studies
  - Pre-clinical, clinical trials, observational studies
- Published Literature
- Unpublished data
  - Sponsors, other regulators, healthcare professionals

Who Reports?



- Nurses
- Community pharmacists
- Hospital pharmacists
- Hospital doctors
- GPs
- Other
- Public
- Other healthcare professionals

2016

Spontaneous Reporting - Strengths

- Proven to identify new reactions
- Sensitivity is potentially high
- Inclusive (all medicines for life)
- Can be rapid
- Can be applied widely
- Fairly cheap
- Harnesses the reporter's intelligence

Spontaneous Reports - Weaknesses

- Under reporting
- Poor for certain reactions
- Frequency of reaction can’t be determined
- Uncertainty regarding causality
- Data can be misinterpreted/abused
- **Beware** of stimulated reporting

Tools for Detecting Signals from Spontaneous Reports

- Individual case analysis – WHO causality criteria
- Seriousness
- Trend analysis
  - Reporting rates
  - Reaction profile
  - Data mining- Proportional reporting ratio (PRR)

Causality assessment

- Temporal relationship (including dechallenge/rechallenge)
- Alternative causes
- Nature of event (skin reactions)
- Plausibility (class effect, pharmacology)

Beware of the Nocebo Effect

Skin reaction to vaccination before injection

Every time an injection was given the girl had an immediate significant rash on her arm.

Her mother (a doctor) took her to hospital to give the next HPV-injection.

When approaching the site with an injection needle, the mother witnessed the appearance of an all too familiar rash. The skin reacted in anticipation before the needle even touched it.

doi.org/10.1016/j.vaccine.2009.12.044

Seriousness

- Highlight and prioritise
- Proportion of serious events does not reflect safety
- Determined based on what happens to patient – no impact on causality
- Criteria (ICH E2D)-
  - Death
  - Life-threatening (real not hypothetical)
  - Hospitalisation (or prolongation)
  - Persistent or significant disability
  - Birth defect
  - Medically important (intervention- agreed lists)

Reporting Rates

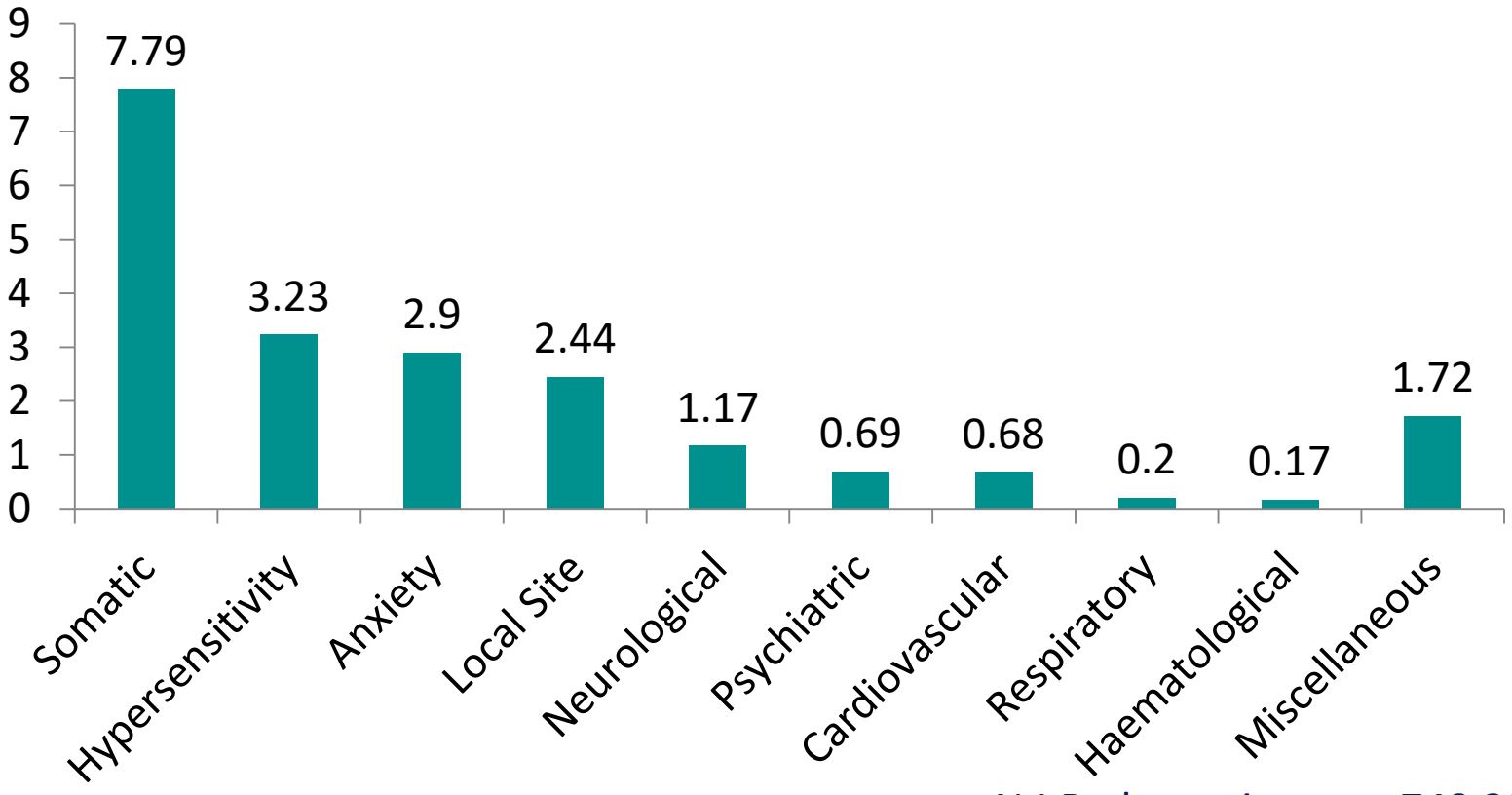
Influenza vaccine hypersensitivity (HS)

www.medsafe.govt.nz/safety/EWS/2015/influenza-vaccine-hypersensitivity.asp

Year	HS Reactions	HS Reports	Total Influenza Reports	HS/ Total Reports %
2011	79	53	209	23.4
2012	79	58	197	29.4
2013	146	101	292	34.6
2014	110	75	255	29.4
2015 (to 20 May)	76	53	144	36.8

Reaction Profile

Crude AEFI rate per 10,000 doses of **Gardasil** from CARM reports 2008 to 2017



N.I.R. denominator = 749 383

Data mining

Medicine	Reaction (MedDRA PT)	listed in data sheet?	No. of cases	No. medicine-reaction reports	PRR
Influenza vaccine	Pain in extremity	1	1	8	18.9
Gardasil	Fatigue	1	1	25	2.5
Gardasil	Muscle contractions	0	1	6	3.4
Gardasil	Muscle twitching	0	1	4	9.0
Gardasil	Tremor	0	1	12	1.4
Gardasil	Muscle spasticity	0	1	2	22.7
Gardasil	Hallucination	0	1	2	0.4
Prevenar 13	Somnolence	1	1	17	7.4
RotaTeq	Irritability	0	1	13	9.2
RotaTeq	Pyrexia	1	3	23	4.4
RotaTeq	Rash macular	1	1	8	10.7
RotaTeq	Somnolence	0	1	9	6.0
RotaTeq	Urticaria	1	1	12	1.8
RotaTeq	Vomiting	1	3	30	7.3