

Adverse events following Immunisation: From notification to interpretation

Federal Agency for Medicine and Health Products

6 December 2019

Agenda

- Vaccinovigilance: quick overview
- Causality assessment
 - spontaneous reporting
 - signal assessment
- Messages to take home



Vaccine Pharmacovigilance

Quick overview



Vaccinovigilance

What is well documented for new vaccines:

- Quality aspects
- Immunogenicity
- Reactogenicity
- Safety profile

Table 1 — Chance that a very rare side-effect (0.01%) will not be observed

Number of patients treated	Chance of missing (%)
500	95.1
1000	90.5
2500	77.9
5000	60.7
7500	47.2
10000	36.8
15000	22.3
20000	13.5
25000	8.2
30000	5.0

What needs follow up:

- **Rare or delayed** adverse events
- Safety in **populations not included** in clinical trials
- Adverse events due to **administration errors**
- Adverse events due to « **off-label** » use of the vaccine

Vaccinovigilance

❖ How do we detect new adverse events?

Passive pharmacovigilance:

- Spontaneous case reporting (yellow cards)
- Registries

Active pharmacovigilance

- Forms

Studies at population level

- Epidemiological studies in population or in databases



Passive Surveillance: Spontaneous Reporting



**Vaccinees
and families**
> July 2012



**VACCINATORS and
HEALTH Care professionals**



The registration is mandatory

- Severe AEs (<15d)
- Non severe AEs (<90d)



ADRreports.eu



VigiBase

Vigiaccess.org

What should be notify?

Any **suspected** adverse event that is:

- **Serious**: death, compromised live prognosis, hospitalisation, invalidity or incapacity, birth defect, or any **medically significant** event
- **Unexpected**: by its nature, severity, frequency or evolution (= not conform to SPC)
- **Suspect**: known but the frequency, severity or outcome is not as expected
- **Administration errors**

Causality should not be demonstrated to notify the event



SPONTANEOUS REPORTING IN BELGIUM

Vaccines only

	Children	Adults
Within calendar	989	410
Outside calendar	128	273
Influenza pandemic	7	164
Total	1,116	832

Period: 01.01.2009 to 31.12.2018 (10 years)

Source: Eudravigilance

Children: <18 years

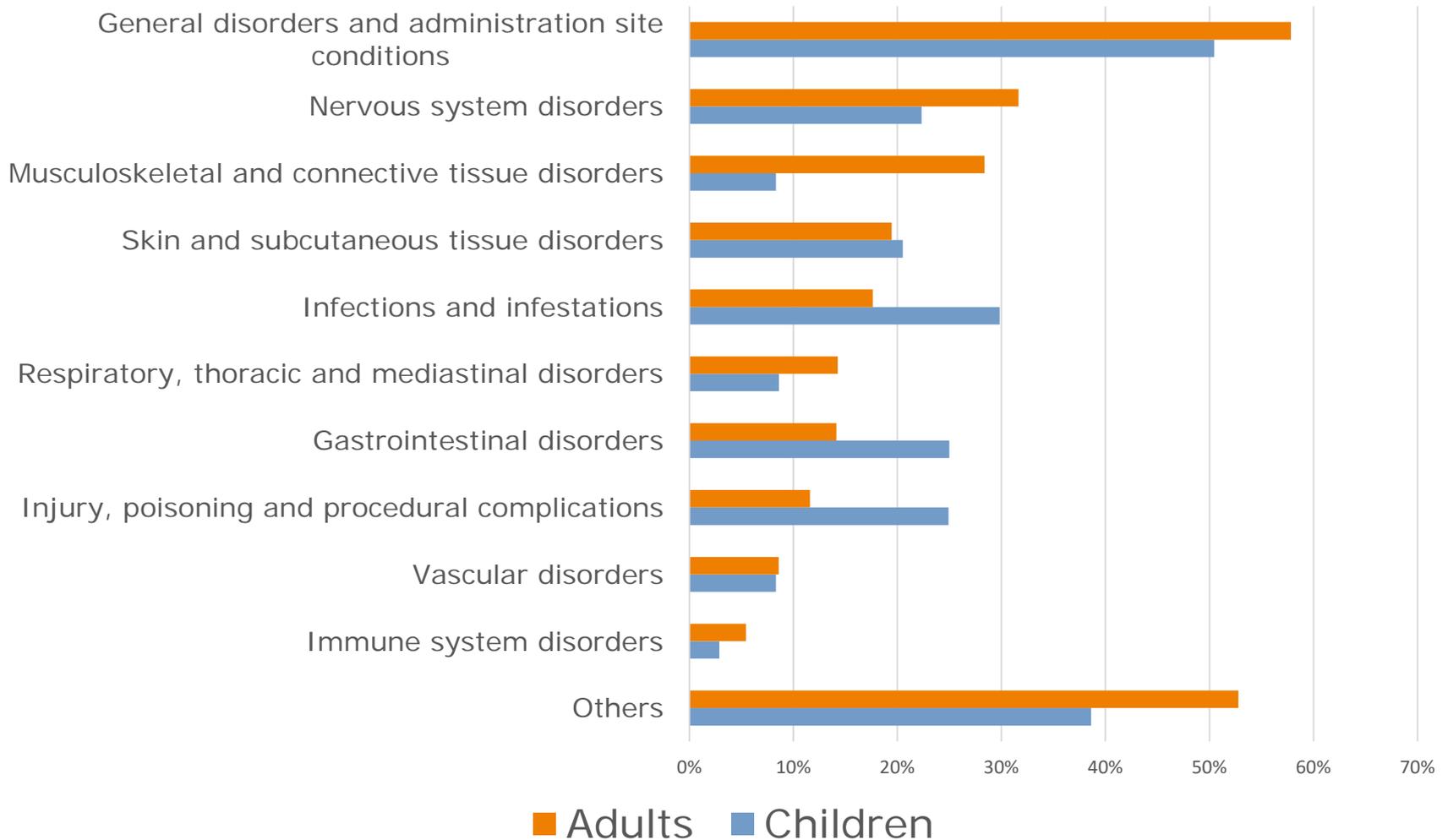
Within calendar, children: P-D-T-P-Hib-HVB, Pn, Rota, MMR, MenC, HPV

Within calendar, adults: Flu, Pn, D-T-P

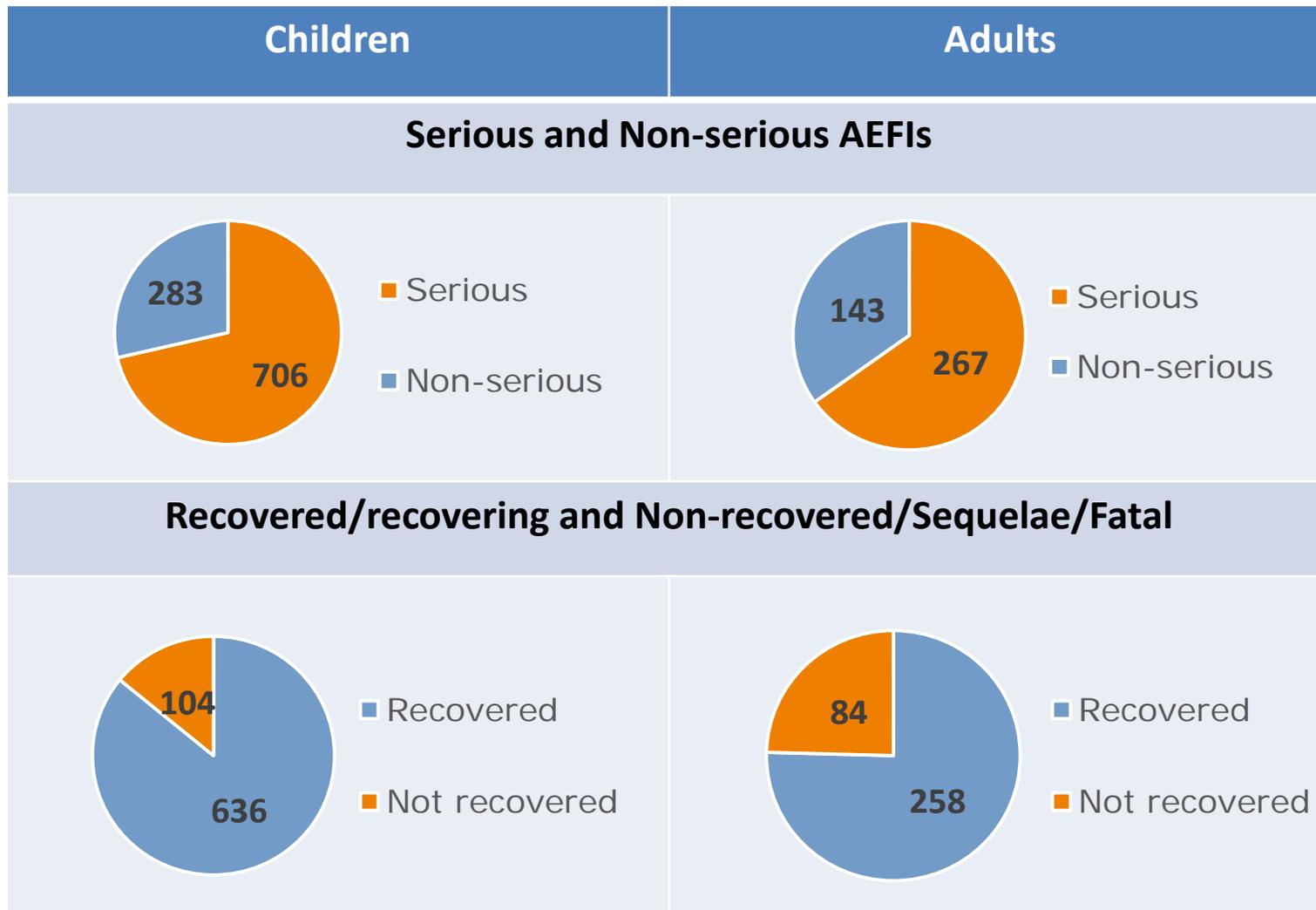


SPONTANEOUS REPORTING

Distribution by System Organ Class (SOC)

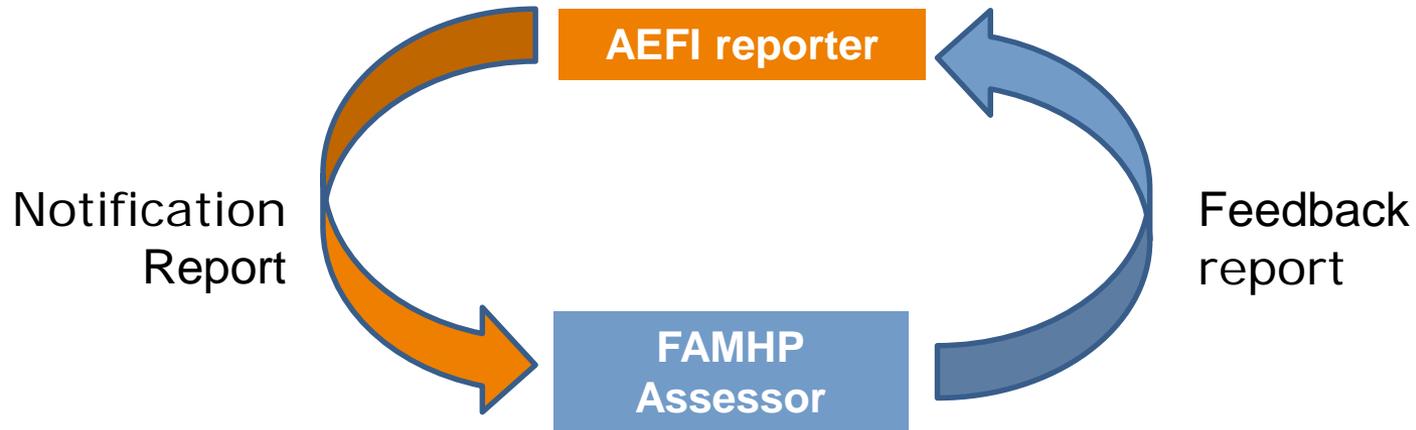


SPONTANEOUS REPORTING IN BELGIUM



Causality Assessment

1) Assessment of an individual report



2) Assessment of a signal



- **Review of cases**
- **Review of other sources:** literature, epidemiological studies, sc. advisory group, etc.

Causality assessment & Individual reports



CAUSALITY CATEGORIES (WHO-UMC)

Causality term	Assessment criteria (simplified)
(1) Certain	Plausible time relationship Other cause(s) excluded Mechanism plausible, recognised phenomenon
(2) Probable/likely	Reasonable time relationship Other cause unlikely
(3) Possible	Reasonable time relationship Other cause possible
(4) Unlikely	Time relationship improbable Other cause provides plausible explanation
(5) Unclassified	More data are expected (temporary code)
(6) Unclassifiable	Information insufficient or contradictory

https://www.who.int/medicines/areas/quality_safety/safety_efficiency/WHOcausality_assessment.pdf



Report N° 1

9 years old female

Date of vaccination: 21.03.2019 – Men B vaccine

Start: 22.03.2019

AE: intense pain the day after MenB vaccination in thigh. Impossibility to fold or move leg.

Treatment: improvement with Nurofen Sirop

Outcome: full recovery at day 4

End: 24.03.2019

Causality assessment N° 1

1. **Temporal association:** start the day after
2. **Other causes:** no other treatment or cause reported
3. **Phenomenon recognised:**

- SPC and Micromedex: pain at injection site, hypotonia, arthralgia listed
- Vigibase: 187 reports of 'incapacity to walk'

→ Code 1



Report N° 2

67 years old female

Date of vaccination: 10.10.2016 - Inactivated influenza tetra

Other treatments: polymedication

Start: 05.12.2016

AE: vasculitis

Treatment: unknown

Outcome: not resolved

End: ongoing (reported October 2017)

Causality assessment N° 2

1. Temporal association: 2 months
2. Other causes: co-morbidities suspected but not reported
3. Phenomenon recognised:
 - SPC : not listed
 - Micromedex: Listed
 - Vigibase: 303 reports associated to flu vaccination

→ Code 3



Report N° 3

41 years old female (pregnant)

Date of vaccination: 25.01.2019 - DTP

Other treatments: none reported

Start: 26.01.2019

AE: pre-eclampsia at 6 month of pregnancy, high HBP + oedemas

Treatment: cesarian section

Outcome: highly prematured baby

End: - (reported in April 2019)

Causality assessment N° 3

1. Temporal association: the day after
2. Other causes: age of the patient, no treatment taken
3. Phenomenon recognised:
 - SPC + Micromedex: not reported
 - Literature: does not support a risk of pre-eclampsia (cohort study in New-Zeeland)
 - Vigibase: pre-eclampsia (17), gestational HBP (5), HBP (167) for DTC vaccines

→ Code 6

Advances and Limitations of Standardised Case Causality Assessment

What causality assessment can do	What causality assessment cannot do
Common understanding among assessors	Cannot prove connection between vaccine and event
Classify relationship likelihood	Give accurate quantitative measurement of relationship likelihood
Mark individual case reports	Change uncertainty into certainty

From WHO - Upsala Monitoring Center

https://www.who.int/medicines/areas/quality_safety/safety_efficiency/WHOcausality_assessment.pdf



Causality assessment & Safety Signals



Safety signal

A safety signal is information on a new or known adverse event that **requires further investigation**.

Safety signals may be detected from a **wide range of sources**.

The presence of a safety signal **does not** necessarily **mean** the vaccine **has caused** the reported adverse event.

The assessment of safety signals establishes whether or not there is a **causal relationship** between the vaccine or the reported adverse event.

The evaluation of safety signals is part of **routine pharmacovigilance**.

Source: EMA website





Safety Signal Causality Assessment

Detection

- Individual reports: Yellow cards
 - Registers: pregnancy registers,
 - Forms: systematic documentation of AEFIs
 - Studies in population
 - Literature
-

Assessment:

- Review of individual reports
 - Studies at population level
 - Observed versus expected studies
 - Epidemiological studies
 - Mechanistic studies, non-clinical data
-

Understanding:

- Strength of the association
 - Specificity, temporal association
 - Level of evidence
 - Biological plausibility
-

Actions

- Request for additional data
- Request for risk minimisation measures
- Communication
- Regulatory measures



Signal assessment : review of individual cases

- **Case definition:**
 - symptoms, signs, tests
 - level of confirmation
- **Terms of extraction** from the database
- **Temporal relationship** - period of risk
- **Specificity** = identification of other causes



Systematic review of all reports according
to a standardised protocol

Messages to take home



Messages to take home

- The role of vaccine pharmacovigilance is to detect and assess AEFIs and safety signals. This is a continuous process after the authorisation of a vaccine.
- A definite causal association or absence of association often cannot be established for an individual event (WHO).
- A causality should not be demonstrated to notify an event.
- But it is important to provide complete information to allow further assessment.



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A large, stylized graphic of a human eye, rendered in light blue and grey tones, serves as the background for the central text. The eye is composed of a large outer arc, a smaller inner arc, and a central circular pupil area.

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