COVID-19 vaccines:
AEFI/ AESI routine surveillance activities

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Global goals of COVID-19 vaccine safety surveillance - reminder

- **Detect serious adverse event following immunization (AEFIs)/ adverse events of special interest (AESIs) rapidly** in order to provide **timely data** that can be shared with relevant stakeholders for action
- Generate data to **characterize the safety profile** of the COVID-19 vaccines in use
- Help to **monitor the acceptable benefit-risk ratio** throughout the COVID-19 vaccine life-cycle
- **Identify, investigate, assess and validate safety signals** and recommend appropriate public health or other **interventions**
- Maintain public and stakeholder **confidence in vaccines** and immunization by ensuring high quality safety surveillance

Surveillance concepts – routine pharmacovigilance

- **Routine** pharmacovigilance is the **primary/minimum** set of activities required for all medicinal products/ vaccines
- National Regulatory Authorities and Marketing Authorisation Holders are responsible for **monitoring** the **safety** of the medicinal products/ vaccines
- Role and responsibilities should be defined at country level
- Routine activities
  - **Routine passive safety surveillance** (’spontaneous reporting’)
  - **Signal detection**: important element in identifying new risks
  - Observed *versus* expected analysis*
    - observed rates of AEs compared with the expected rates available from the scientific literature
  - Periodic cumulative reviews

*https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5063172/

Routine pharmacovigilance activities should be put in place for the surveillance of:

- serious AEFI/ AESI;

- batch-related reactions (including the measures taken to clearly identify the name of the product and the batch number);

- potential interactions with co-administration of other vaccines,

- any AESIs identified as an important potential risk

- inappropriate use of vaccines

- reports of vaccination failure

- potential immunisation errors

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-i-vaccines_en.pdf

Routine pharmacovigilance activities in the context of the COVID-19 pandemic to be implemented by the Marketing Authorisation Holders

- Included in the Risk Management Plans (refer to tomorrow's presentation)
  - Targeted follow-up questionnaires
    - to obtain structured information on reported AESI

- *Note*: Additional safety surveillance activities such as PASS/ vaccine safety studies should be carried out by MAH to continue collecting information on safety beyond that collected during pre-licensure COVID-19 vaccine trials (next presentation)

Routine passive safety surveillance ('spontaneous reporting')

- The **fundamental**, basic type of surveillance for all immunization strategies, relatively inexpensive
- Cases are not actively sought
- Identifies events (AEFIs including AESIs) that are temporally associated with immunization and performs investigation/ causality assessment
- Electronic or paper-based system

Routine passive surveillance

- Aims to:
  - **detect safety signals for further evaluation** (sometimes also from media reports and public concerns)
  - **identify rare AEFIs**
  - **identify immunization-error related adverse reactions**
  - assess reporting of **clusters**
- **Who** is involved?
  - Reporters: health care workers, peripheral health staff, nurses, doctors, patients, parents, etc.
  - National stakeholders: regional pharmacovigilance centers, National regulatory authorities, Ministry of Health, Expanded programmes on immunization and national immunization programmes…
  - Marketing Authorisation Holders

Routine passive surveillance

- **Limitations:**
  - **Underreporting**

  - **Not sufficient** for rapid assessment and appropriate public health response in COVID-19 pandemic

- All countries should strive to strengthen their routine passive surveillance capacities

- For countries with advanced safety surveillance systems:
  - Implement **active surveillance** systems to improve detection of AEFIs

Strengthening of routine passive AEFI surveillance

Training on identification and reporting of AEFI for healthcare workers

Update, print and distribute AEFI surveillance tools

Innovate processes for timely reporting, review and data sharing nationally, regionally and globally

Stimulate AEFI reporting and perform real time safety data analysis

Develop Standard Operating Procedures for the coordination process between NRA, NIP/EPI and other institutions with responsibilities for AEFI surveillance

Consider coordination of activities with Public Health Emergency Units

Consider setting up AEFI committees at subnational level as well as national level particularly in large countries

Example - Polio vaccine (nOPV2)

- Once a country decides to use nOPV2: passive AEFI surveillance and AFP surveillance should already be ongoing before nOPV2 use (nOPV2 Vaccine Deployment Readiness Checklist)
- Acute Flaccid Paralysis (AFP) cases surveillance
  - AFP cases are reported to local government area-level surveillance officers by health facility staff or a network of trained community members.
  - Surveillance officers also perform active case finding at traditional and non-traditional healthcare locations.
  - When an AFP case is identified, surveillance officers perform detailed case investigations
- In addition to AFP surveillance, countries perform routine passive surveillance for all adverse events following immunization (AEFI)
  - involve both National Regulatory Authorities (NRA) and National Immunization Programs and follow a process of case identification, reporting, and investigation separate from the AFP surveillance system

Guide for Surveillance of Adverse Events of Special Interest (AESI) during novel Oral Polio Vaccine type 2 (nOPV2) Use
https://polioeradication.org/wp-content/uploads/2020/11/EN-nOPV-AESI-surveillance-guide.pdf

Signal Detection (SD)

- Signal: **information** that arises from **one or multiple sources** 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 verification

- This potentially includes all scientific information concerning the use of medicinal products and the outcome of the use (i.e., quality, non-clinical and clinical data (including pharmacovigilance and pharmacoepidemiological data))

- Common sources for signals include spontaneous reporting systems, active surveillance systems, studies and the scientific literature reporting such data

- Signal detection is often based on the periodic monitoring of safety databases. However, all relevant sources should be considered during signal management

Methods of signal detection

- **Review of case reports**
  - Review of individual cases or case series (especially AESI)
  - Periodic aggregate review of spontaneous reports (cumulative reviews)
    - review of periodic safety update reports (PSURs)/ Monthly Safety Reports prepared by Marketing Authorisation Holders

- **Literature review**

- **Tracking of potential signal** through rumors, media, social media, other PV systems, WHO, EMA, FDA websites

CIOMS **Practical Aspects of Signal Detection in Pharmacovigilance** https://cioms.ch/wp-content/uploads/2018/03/WG8-Signal-Detection.pdf
Analytics in VigiLyze: https://www.who-umc.org/vigibase/vigilyze/analytics-in-vigilyze/
https://www.who-umc.org/media/164041/measures-of-disproportionate-reporting_2016.pdf

Methods of signal detection

- **Quantitative signal detection (disproportionality methods)**
  - Automated screening of adverse events databases (e.g., VigiLyze)
  - Various different ways to calculate disproportionality
    - frequentist methods such as the reporting odds ratio (ROR) or the proportional reporting ration (PRR)
    - Bayesian methods such as the Empirical Bayes Geometric Mean (EBGM) and the **Information Component (IC) => Vigilyze**.

- Signal detection ≠ signal confirmation

CIOMS **Practical Aspects of Signal Detection in Pharmacovigilance** https://cioms.ch/wp-content/uploads/2018/03/WG8-Signal-Detection.pdf
Analytics in VigiLyze: https://www.who-umc.org/vigibase/vigilyze/analytics-in-vigilyze/
https://www.who-umc.org/media/164041/measures-of-disproportionate-reporting_2016.pdf

COVID-19 vaccine – safety signal (1)

- Review of thromboembolic events with COVID-19 Vaccine AstraZeneca is being carried out in the context of a safety signal
- 2 cases reported in Austria
  - a person was diagnosed with multiple thrombosis (formation of blood clots within blood vessels) and died 10 days after vaccination
  - another was hospitalised with pulmonary embolism (blockage in arteries in the lungs) after being vaccinated
- As of 10 March 2021, 30 cases of thromboembolic events had been reported among close to 5 million people vaccinated with COVID-19 Vaccine AstraZeneca in the European Economic Area
- EMA's safety committee PRAC is reviewing this issue (extraordinary meeting 18-March-2021)

https://www.ema.europa.eu/en/news/investigation-covid-19-vaccine-astrazeneca-thromboembolic-events-continues

COVID-19 vaccine – safety signal (2)

- Assessment of a safety signal regarding cases of anaphylaxis (severe allergic reactions) with COVID-19 Vaccine AstraZeneca

  Review of 41 reports of possible anaphylaxis seen among around 5 million vaccinations in the United Kingdom

  PRAC considered that a link to the vaccine was likely in at least some of these cases

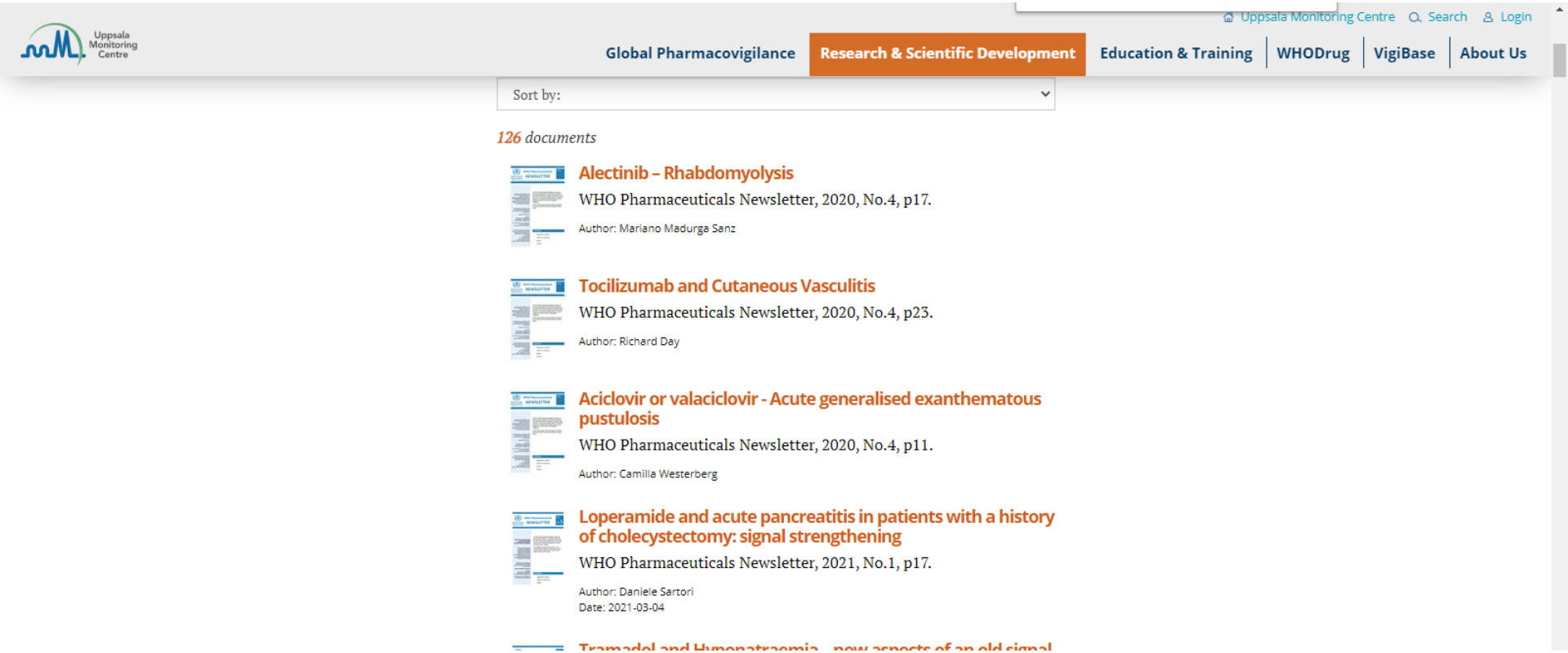
  PRAC has recommended an update to the product information to include anaphylaxis and hypersensitivity (allergic reactions) as side effects and to update the existing warning to reflect that cases of anaphylaxis have been reported

https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-8-11-march-2021

Examples - signal detection by WHO

- Uppsala monitoring Center (UMC) performs periodic screenings of VigiBase (statistical screening) to identify safety signals
- Pharmacovigilance experts at UMC and experienced scientists and clinicians from the UMC Signal Review Panel, assess the clinical evidence and decide whether or not it is strong enough to represent a signal
- A library of all the signals published in the WHO Pharmaceuticals Newsletter since 2012

Examples - signal detection by WHO



Aciclovir or valaciclovir - Acute generalised exanthematous pustulosis (AGEP)

Uppsala Monitoring Centre

- Aciclovir is an antiviral drug used to treat herpes simplex and zoster infections
- Acute generalised exanthematous pustulosis (AGEP) is a severe skin reaction, characterized by an acute onset (less than 10 days and typically within 48 hours) of mainly small non-follicular pustules on an erythematous base.

1. Routine signal detection screening of VigiBase: **disproportionality reported**

2. Review of cases in Vigibase

Case	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA PT)	Biopsy or patch test result	TTO	Action taken with drug	Outcome	Comment
1	75/M	Aciclovir*, Solifenacin* (S) *Concomitant lisinopril, nitrendipine, solifenacin; tamsulosin mentioned in the published case report*	AGEP, Erythema, Swelling	Skin biopsy proved drug induced reaction	-	Drug withdrawn/ *unknown outcome*	Unknown	Published case report describes aciclovir as treatment for the reaction and points to solifenacin as prime suspect
2	68/F	Aciclovir* (S) Alprazolam, Budesonide;Formoterol, Lercanidipine, Metformin, Simvastatin, Venlafaxine* (C)	AGEP	-	1 days	-	Recovering	TTO seems to have been 2 days. No dates reported for concomitant drugs
3	70/M	Aciclovir*, Benzylpenicillin, Gabapentin*, Olanzapine (S)	AGEP	-	3 days	-	Recovering	Both benzylpenicillin and gabapentin were started after aciclovir (TTO 1 and 0 days).
4	26/F	Aciclovir* (S), Dexamethasone (C)	AGEP	-	11 days	Drug withdrawn/	Recovering	TTO probably shorter since narrative states that eruptions

3. Review of the Literature and labelling

4. Conclusion: Signal confirmation – May required further investigations (studies)

Signal detection COVID-19 Vaccine Moderna

Table 29: mRNA-1273 Vaccine Signal Data Sources and Frequency of Evaluations

Data Source	Frequency of Safety Evaluations
Company global safety database	Ongoing monitoring of individual cases of Suspected Unexpected Serious Adverse Reaction (SUSAR), safety concerns, and Adverse Events (AE) of Special Interest. Weekly aggregated review of AE cases for trend analyses. Review of disproportionate reporting of preferred terms (PT) during a time interval as compared to all data prior to the RP for the mRNA-1273 vaccine. Review of endpoints of interest (ie, case counts, demographics, country of origin, time to onset, seriousness, batch numbers, fatalities, AE from the product surveillance list of safety topics and based on MedDRA system organ class and high-level term, and identification of potential clusters of Individual Case Safety Reports (ICSRs).
Literature	Weekly literature review. Any literature abstract or article signal detection run will be reviewed.
EudraVigilance	Continuous monitoring. Biweekly critical review of the EudraVigilance data analysis system using available reports (ie, Electronic Reaction Monitoring Reports [e-RMRs] and active substance groupings, ICSR line listings and ICSR forms).
VAERS	Frequency of review will depend on public availability of redacted VAERS extracts. Current estimates based on public communication as well as processing time indicate this frequency will range between every two to four weeks. Generation of disproportionality scores using Empirical Bayesian Geometrical Mean and its 90% confidence intervals after new uploads of Vaccine Adverse Event Reporting System extracts in Empirica Signal.
Health Authorities websites	Ongoing review of data published on the Safety Web Portals of selected major regulatory agencies to identify required actions regarding the product and similar products.

What routine activities your country will adopt for COVID-19 vaccine safety surveillance during the pandemic?

Thank you