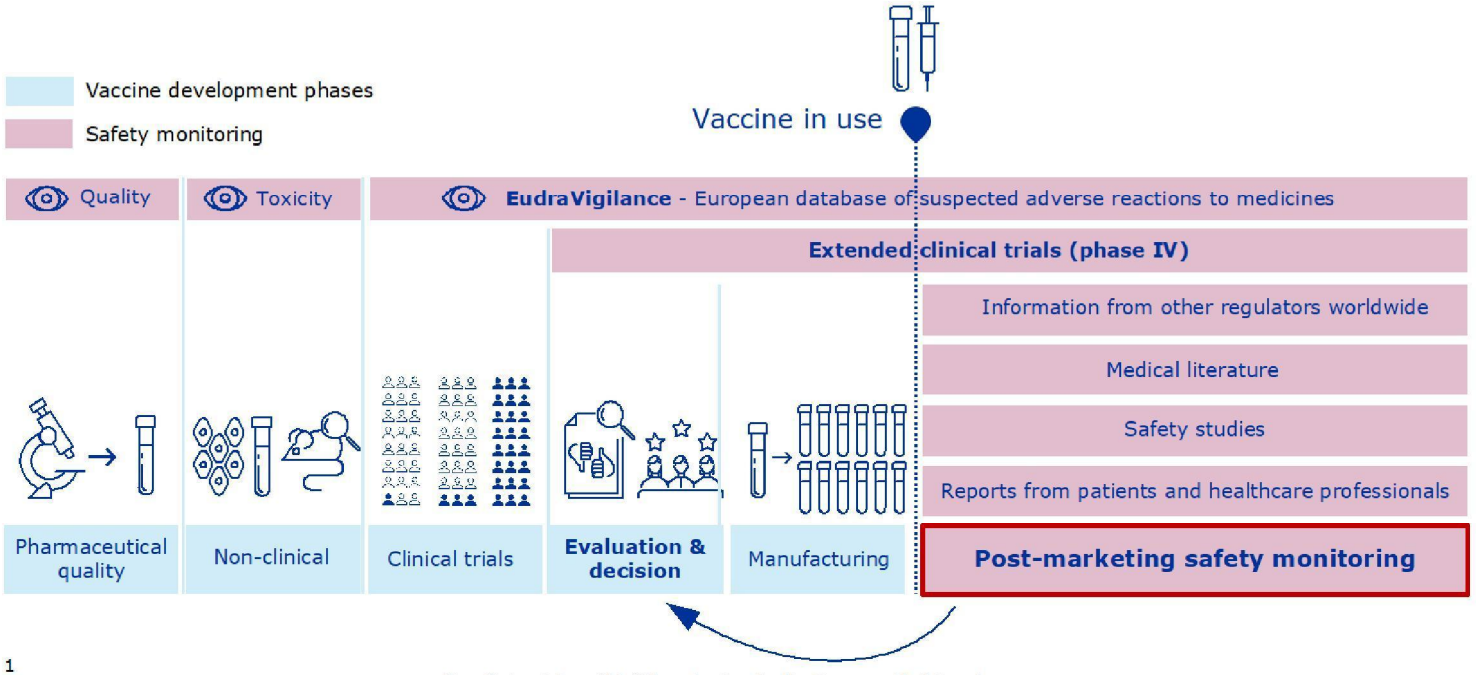
Observational COVID-19 vaccine safety studies: preparedness, ongoing and planned studies

EU-EEA NITAG collaboration webinar on COVID-19 vaccine safety

Presented on 04 February 2021 5.1.2e

5.1.2e

Monitoring vaccine safety in real-life through observational studies



Safety monitoring of COVID-19 vaccines

Preparedness: ACCESS project

EU infrastructure for vaccine monitoring
- Background incidence rates of adverse events of special interest (AESIs)
- Protocol templates for safety and effectiveness studies
- EU network of secondary data sources for COVID-19 vaccine monitoring, and other tools

Now: Early study

Early safety monitoring to complement spontaneous reporting systems (2021)
- Priority groups, ~10 months duration, 7 MS (Germany, Croatia, NL, Belgium, Luxembourg, Italy, France) + UK
- Hypothesis-generating
- App-based primary data collection: incidence rates of suspected adverse reactions; observed-to-expected analyses
- Complemented by monitoring in healthcare databases (AESIs, vaccine exposure, COVID diagnoses, selected ADRs)

EC funding 2021-2022

Joint ECDC/EMA vaccine monitoring programme
- Observational safety studies procured by EMA (effectiveness studies: ECDC)
  1) Active prospective surveillance and signal strengthening activities, 2 years, at least 10 additional MS
  2) Hypothesis-testing, etiological studies to evaluate and quantify safety signals: assumption for 10 potential safety signals to be investigated over 2 years

Contract with EU PE & PV Research Network (Utrecht University) for both ACCESS project and early safety study

Preparedness

Background incidence rates

- Incidence of new cases in non-exposed population
- Assist in distinguishing events potentially vaccine-attributable from events temporally associated
- Need for standardised case definitions. Brighton collaboration definitions preferred, importance of case validation
- Concomitant risk factors act as confounders (gender, age, genetic predisposition, geography, changing epidemiology, standard of care, special population)
- Challenging for rare (<1/1,000 PY) or very rare (<1/10,000 PY) diseases

- ACCESS: background rates of AESIs in 7 countries publicly available, stratified by database (country), age, gender, co-morbidity, year
- Data from IMI ADVANCE (2003-2014): 5.1.2e
  1.2 et al., *Drug Saf*. 2021 Jan 19

- What if new safety concern?
  - Rapid generation of new background rates (EMA in-house databases or via framework contracts)
  - Observational studies
  - Literature

Other ACCESS deliverables

- **Protocol** templates for COVID-19 vaccine **safety** studies:
  - Prospective cohort-event monitoring (active surveillance)
  - Rapid assessment using healthcare databases (ecological or self-controlled methods)
  - Signal evaluation (hospital-based or healthcare databases)
- **Protocol** templates for COVID-19 vaccine **effectiveness** studies
  - Retrospective cohort study using healthcare databases
  - Hospital-based study (test-negative case-control design)
- **Visualisation** of coverage, benefits and risks
- **Protocol** for monitoring vaccine **coverage**
- **Feasibility** analysis of an EU infrastructure for COVID-19 vaccine monitoring

EC funding 2021-2022

Joint ECDC/EMA COVID-19 vaccine monitoring programme

- Nov. 2020: EC adopted a proposal to **strengthen EMA and ECDC mandates** in response to learnings from the COVID-19 pandemic

  → Creation of a **European Health Union**, empowering the two agencies to jointly coordinate independent vaccine monitoring activities

- Safety studies procured by EMA through its framework contracts (effectiveness/impact: ECDC)
- Jointly managed vaccine monitoring platform with **joint Advisory Board** to oversee prioritisation and advise on design, implementation and interpretation of the studies
  - Membership: representatives from Ministries of Health, National Public Health Authorities, National Medicines Agencies, and experts from relevant EMA committees, the EU NITAG collaboration, and relevant EC services

EC-funded, COVID-19 prospective vaccine safety study (2021/2022)

EC funding 2021-2022

Active surveillance

- Hypothesis-generating, rapid initiation, 2 years → large population, capture potential long-term effects of the vaccines
- Incidence rates of suspected ADRs and AESIs stratified by vaccine brand and other variables of interest
- Target number of at least 10 MSs not yet included in the early study
- Medical confirmation of severe adverse reactions (SARs) and AESIs
- Suitable comparator group(s) tbd

Signal strengthening

- Further characterise potential safety concerns, provide additional evidence supporting signal management and regulatory decision-making
- Observed-to-expected analyses, case-only analyses, or other appropriate pharmacoepidemiological methods
- Generation of novel background incidence rates as required
- Out of scope: full signal evaluation through hypothesis-testing etiological studies (procured separately, assumption: 10 studies)

Conclusion

- Comprehensive plan for post-authorisation safety monitoring of COVID-19 vaccines through observational research
- Complements spontaneous reporting systems for signal detection (routine pharmacovigilance) and safety monitoring activities ongoing or planned at country level
- Preparedness and capacity for rapid identification of new or changing risk
- Cross-fertilisation: international collaborations (e.g. ICMRA)
- EC-funded 2-year COVID-19 vaccine monitoring plan to lay the grounds for sustainable EU-level vaccine monitoring platform

Link to EMA COVID-19 observational studies
Link to VAC4EU (ACCESS deliverables)
See also EU PAS Register ENCePP Home Page

Thank you for your attention

Questions: 5.1.2e @ema.europa.eu

European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Back up

Pre-defining AESIs for vaccines

- Novel vaccine, vaccine technology/platform
- (S)AEs expected to occur with any vaccine
- Historical relevance / identified risk with "similar" vaccine
- Biological plausibility
- Risk of vaccine-enhanced (respiratory) disease
- Health outcomes in specific (risk) groups: age, special populations, co-morbidities (exacerbation of pre-existing condition)
- Potential risk identified pre-licensure (imbalances, unexpected observed SAEs)
- Preparedness: case definitions, background rates, knowledge of risk factors
- Analysis/interpretation of safety signals for AESIs: specific challenges for rare and late onset AESIs; knowledge (or assumption) of time-to-onset / post-immunisation risk period; specific challenges with secondary data collection; importance of case ascertainment
- Importance of reporting and evaluation: impact on benefit-risk profile, communication

Black S et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet. 2009;374:2115
Chao C, Jacobsen SJ. Evaluation of autoimmune safety signal in observational vaccine safety studies. Hum Vaccin Immunother. 2012;8(9):1302-4

Updated full List of AESIs (SPEAC, WHO, EMA, CDC/FDA

Body System	AESI	SPEAC	WHO	EMA/ACCESS	FDA/CDC
Cardiac	Myocarditis	X	X	X	X
Cardiac	Acute myocardial infarction (AMI)				X
Cardiac	Pericarditis	X			X
Cardiac	Arrhythmia	X	X	X	
Cardiac	Coronary artery disease	X	X	X	
Cardiac	Heart failure	X	X	X	
Cardiac	Microangiopathy	X	X	X	
Cardiac	Stress cardiomyopathy	X	X	X	
Cardiac	Cardiogenic shock	X			
Dermatologic	Chilblain-like lesions	X	X	X	
Dermatologic	Erythema multiforme	X	X	X	
Dermatologic	Single organ cutaneous vasculitis	X	X	X	
Gastrointestinal	Liver injury	X	X	X	
Hematologic	Thrombocytopenia	X	X	X	X
Hematologic	Disseminated intravascular coagulation (DIC)		X	X	X
Hematologic	Venous thromboembolism (VTE) / thromboembolism		X	X	X
Hematologic	Immune thrombocytopenia (ITP)			X	X
Hematologic	Cerebrovascular stroke	X	X		X
Hematologic	Deep vein thrombosis	X	X	X	
Hematologic	Hemorrhagic disease	X			
Hematologic	Limb ischemia	X			
Hematologic	Pulmonary embolus	X			

Body System	AESI	SPEAC	WHO	EMA/ACCESS	FDA/CDC
Neurologic	Acute disseminated encephalomyelitis (ADEM)	X	X	X	X
Neurologic	Guillain Barré Syndrome	X	X	X	X
Neurologic	Encephalitis	X	X		X
Neurologic	Encephalomyelitis	X	X		X
Neurologic	Meningoencephalitis	X	X	X	X
Neurologic	Narcolepsy			X	X
Neurologic	Transverse myelitis			X	X
Neurologic	Convulsion (generalized) (seizures / convulsions)	X	X	X	X
Neurologic	Encephalopathy (not ADEM or TM)				X
Neurologic	Meningitis				X
Neurologic	Myelitis		X		X
Neurologic	Stroke (hemorrhagic and ischemic)		X		X
Neurologic	Anosmia	X	X	X	
Neurologic	Ataxia				X
Neurologic	Chronic inflammatory demyelinating polyneuropathy (CIDP)				X
Neurologic	Multiple sclerosis (MS)			~	X
Neurologic	Optic neuritis (ON)			~	X
Neurologic	Ageusia	X	X	X	
Neurologic	Aseptic meningitis	X			

Body System	AESI	SPEAC	WHO	EMA/ACCESS	FDA/CDC
Immunologic	Anaphylaxis	X	X	X	X
Immunologic	Multisystem inflammatory syndrome in children (MIS-C)	X	X	X	X
Immunologic	Kawasaki disease				X
Immunologic	Autoimmune disease			~	X
Immunologic	Multisystem inflammatory syndrome in adults (MIS-A)				X
Immunologic	Enhanced disease following immunization	X	X	X	
Immunologic	Vasculitides	X			
Musculoskeletal	Acute aseptic arthritis			X	
Musculoskeletal	Arthritis (not osteoarthritis or traumatic arthritis)	X	X		X
Musculoskeletal	Arthralgia (not osteoarthritis or traumatic arthritis)				X
Other	COVID-19 disease			X	X
Other	Sudden death			X	X
Other	Non-anaphylactic allergic reactions				X
Other	Vaccination errors				X
Other	Serious local/systemic AEFI	X			
Renal	Acute kidney injury	X	X	X	
Respiratory	Acute respiratory distress syndrome (ARDS)	X	X	X	X

Body System	AESI	SPEAC	WHO	EMA/ACCESS	FDA/CDC
Pregnancy outcome	Fetal growth restriction			X	
Pregnancy outcome	Gestational diabetes			X	
Pregnancy outcome	Major congenital anomalies		X	X	
Pregnancy outcome	Maternal death		X	X	
Pregnancy outcome	Microencephaly			X	
Pregnancy outcome	Neonatal death		X	X	X
Pregnancy outcome	Preelempsia			X	
Pregnancy outcome	Preterm birth			X	X
Pregnancy outcome	Spontaneous abortion		X	X	X
Pregnancy outcome	Stillbirth		X	X	X
Pregnancy outcome	TOFPA			X	