Monitoring the safety of COVID-19 vaccines using real-world data

PCWP-HCPWP joint meeting, Day 1

01 June 2021

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From early times to expanding safety surveillance activities

2020 ACCESS project

• **Preparedness**
  - Completed

2021 Early study

• **Incidence rates of adverse events**
  - 7 MSs + UK
  - + monitoring in EU healthcare databases

2021-22 Future studies

• **EC funding**
  - Active surveillance
  - Signal strengthening
  - Signal evaluation

Natural history of coagulopathy and use of antithrombotic agents (COVID-19 patients + persons vaccinated against SARS-CoV-2)

Generation of background incidence rates

**New tender**: measuring the association (TE events & TTS)

*TE: thromboembolic events TTS: thrombosis with thrombocytopenia*
• **Background rates of AESIs** from 7 databases in 5 countries: Spain, Italy, UK, Netherlands, Germany, Denmark (+ France available in June) ([Link](https://vac4eu.org/covid-19-tool/))
  
  - Interactive dashboard to visualise background rates: [https://vac4eu.org/covid-19-tool/](https://vac4eu.org/covid-19-tool/)

• **Protocol templates for studies**: safety ([Link](https://vac4eu.org/covid-19-tool/)) and effectiveness studies ([Link](https://vac4eu.org/covid-19-tool/)); coverage of COVID-19 vaccines in healthcare databases ([Link](https://vac4eu.org/covid-19-tool/))

• **Feasibility** of using EU healthcare databases ([Link](https://vac4eu.org/covid-19-tool/)) to report

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*AESIs: adverse events of special interest*
Early safety monitoring study: Feb-Nov 2021

Two work packages:

1) Active surveillance, prospective cohort
   • Vaccinated persons to self-report suspected adverse events using application (→ incidence data)
   • Hypothesis-generating
   • 7 MS (Germany, Croatia, NL, Belgium, Luxembourg, Italy, France) + UK

2) Monitoring in electronic health records
   • Databases in ES, IT, NL, UK
   • AESIs and other adverse events, COVID diagnoses before/after vaccination, vaccinations
   • Additional background rates for embolic and thrombotic events

Link to protocols on EU PAS Register WP1 - WP2
Natural history of coagulopathy and use of anti-thrombotic agents in COVID-19 patients and in persons vaccinated against SARS-CoV-2

- Study initiated in 2020, data by Sept. 2021

- **Cohort of COVID-19 patients**: incidence rates of embolic and thrombotic events following COVID-19 infection

- **Vaccinated cohort**: incidence rates of embolic and thrombotic events within 7-, 14-, 21- and 28 days after vaccination

- Information on age, sex, vaccine, relevant risk factors (e.g. BMI, diabetes, hypertension, pregnancy, malignancy), medication use at time of vaccination

- Healthcare databases in 6 countries (DE, FR, ES, IT, NL, UK) – link to protocol: [EUPAS40414](https://example.com/EUPAS40414)
New study: Association between thrombosis with thrombocytopenia syndrome (TTS) or thromboembolic events, and COVID-19 vaccines

- Association not quantified so far. Objectives:
1) To quantify the association between occurrence of TTS and administration of a COVID-19
2) To quantify the association for thromboembolic events
3) To measure the association between potential risk factors and TTS in vaccinated patients
4) To describe treatments of patients with TTS (anticoagulants, other therapeutic products

Exploratory: To develop a proof-of-concept to support future genetic and pharmacogenomic analyses

- In planning, data by early 2022
Joint ECDC/EMA COVID-19 vaccine monitoring platform

- EMA and ECDC extended mandate

→ European Health Union, joint coordination of independent vaccine monitoring activities

- Joint Advisory Board (EU Commission, national competent authorities, NITAGs*): prioritisation and advice on studies; appraisal of independent data

- Kick-off meeting 26 April 2021

- **Pilot to inform further establishment of sustainable EU platform, building on COVID-19 learnings**

*NITAGs: National Immunisation technical Advisory Groups*
Two-year vaccine safety monitoring study

1) Active surveillance, prospective cohort

- Similar to early study + explore potential longer-term effects of the vaccines + suitable comparators
- At least 10 MSs not included in early study
- General population N≥60,000 (extension of early study)
- Special populations N=60,000 (from other EU projects, incl. children, pregnant women)

2) Readiness & rapid signal assessment

- Rapid pharmacoepidemiological analyses to characterise emerging safety concerns and support signal management
- Common data models, at least 10 electronic healthcare data sources (Netherlands, Denmark, Norway, Spain, Italy, France, Germany, UK)

Anticipated study start: July 2021
Can be adapted to emerging needs and monitoring of new events of interest
Preparedness for signal evaluation → Hypothesis-testing association studies

- Comprehensive pharmacoepidemiological studies to **measure the association** between COVID-19 vaccines and occurrence of specific safety concerns
- Provide **higher level of evidence**: comparisons at individual level, adjustment for confounders, stratification by variables of interest (e.g. risk factors)
- Relative risk (compared to non-vaccinated or other suitable comparator)
- Absolute risk (excess cases)
Covid-19 infectiON and medicineS In pregnancy (CONSIGN)

• Very little/no information to date as pregnant women mainly excluded from COVID-19 clinical trials
  → Guide evidence-based decision-making about COVID-19 vaccine indications, vaccination policies, and treatment options

• Objectives:
  ✓ **Assess use of medicines** for COVID-19 treatment in pregnant women and compare with non-COVID-19/non-pregnant women of same age
  ✓ **Describe severity and clinical outcomes of COVID-19 disease** in pregnant women and compare to non-pregnant women of reproductive age with COVID-19
  ✓ To **assess and compare pregnancy and neonatal outcomes** in different treatment groups of pregnant women
  ✓ To **establish collaborations** with other global initiatives (ICMRA) and have sustainability

• **Ultimately:** Worldwide infrastructure to study medicines in pregnancy beyond COVID-19
Lessons learned from preparedness activities

**Challenges**
- Background incidence rates of adverse events
- Quantifying associations between vaccines and adverse events
- Use of existing databases (data on vaccines, case validation, data source heterogeneity, time needed to obtain data, availability of lab data)
- Case definitions (TTS!)
- Impact of pandemic on healthcare systems

**Opportunities**
- Early preparation was absolutely needed (vaccination start in Dec. 2020)
- Prospective monitoring: apps, near-real time surveillance
- Value of large healthcare databases (sample size, hospital data, common data models, speedy analyses possible)
- Value of EMA framework contracts
- Consortia with demonstrated capacity/expertise
- International collaborations with other regulators
- Lessons learnt from H1N1 flu pandemic
Link to overview of observational COVID-19 research on the EMA website:

Monitoring of COVID-19 medicines

- Safety monitoring of COVID-19 vaccines in the EU (new)
- Natural history of coagulopathy and use of anti-thrombotic agents in COVID-19 patients and COVID-19 vaccine recipients
- Early safety monitoring of COVID-19 vaccines
- Impact of COVID-19 infection and medicines in pregnancy
- Building a framework for the conduct of multicentre cohort studies on the use of medicines in COVID-19 patients
- Preparing an infrastructure for the monitoring of the coverage, safety and effectiveness of COVID-19 vaccines
Thank you for your attention