Evaluation of adverse event clusters following immunization with mRNA COVID-19 vaccines: a real-world analysis using EudraVigilance data

First published: 16/09/2021

Last updated: 05/06/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS43083

Study ID

48901

DARWIN EU® study

No

Study countries

☐ Portugal

Study description

This study is designed as a retrospective observational analysis using individual case safety reports (ICSRs) submitted to EudraVigilance, the European pharmacovigilance database maintained by the European Medicines Agency. It aims to characterize and explore patterns of adverse events following immunization (AEFI) associated with mRNA COVID-19 vaccines, namely Pfizer/BioNTech (Comirnaty) and Moderna (Spikevax), within the European Economic Area.

The main objective is to identify clusters of AEFI based on their frequency of co-occurrence, using descriptive statistics, co-occurrence network analysis, and correspondence analysis. Reports from 1 January 2020 to 31 December 2023 will be retrieved, and no exclusion filters will be applied, ensuring a comprehensive dataset. Analyses will also stratify patterns according to seriousness and age groups.

This study is expected to enhance understanding of safety signals related to mRNA COVID-19 vaccines, inform pharmacovigilance practice, and support the continued assessment of vaccine safety profiles under real-world conditions.

The methodology will comply with STROBE guidelines and the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

Study status

Ongoing

Research institutions and networks

Institutions

Porto Pharmacovigilance Centre, Faculty of Medicine, University of Porto (UFPorto)

Portugal

First published: 17/11/2010

Last updated: 12/06/2023

Institution | Educational Institution | ENCePP partner

University of Porto

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Educational Institution

Faculty of Medicine

Contact details

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Study timelines

Date when funding contract was signed
Actual: 15/09/2021

Study start date
Planned: 01/10/2021

Actual: 01/10/2020

Data analysis start date
Planned: 01/01/2024

Date of final study report
Planned: 19/02/2025

Sources of funding

- EU institutional research programme

More details on funding

Portuguese national funds and Community funds from the European Social Fund (ESF) through FCT – Fundação para a Ciência e a Tecnologia (Portugal)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Drug utilisation

Data collection methods:

Secondary use of data

Study design:

Retrospective observational study using individual case safety reports (ICSRs) from EudraVigilance, analysing adverse event patterns following mRNA COVID-19 vaccination in adults, through co-occurrence and correspondence analysis.

Main study objective:

To characterize and identify clusters of adverse events following immunization (AEFI) with mRNA COVID-19 vaccines in real-world settings, using EudraVigilance data, and to assess the variability in safety profiles between different vaccine versions and across population subgroups.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

COMIRNATY

SPIKEVAX

Anatomical Therapeutic Chemical (ATC) code

(J07) VACCINES

VACCINES

(J07BN01) covid-19, RNA-based vaccine

covid-19, RNA-based vaccine

Population studied

Short description of the study population

This study will include individuals aged 18 years and older who have been recipients of at least one dose of an mRNA COVID-19 vaccine (Pfizer/BioNTech

or Moderna) within the European Economic Area.
The population will comprise all cases reported to EudraVigilance between 1 January 2020 and 31 December 2023 that include at least one suspected adverse event following immunization (AEFI).
No exclusions based on demographic characteristics or comorbidities will be applied.
The study population is expected to reflect a wide range of real-world vaccine recipients, including younger adults (18–45 years), middle-aged adults (46–64 years), and elderly individuals (65 years and older), thus allowing subgroup analyses across distinct age ranges and seriousness profiles of AEFI.

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Special population of interest

Hepatic impaired

Immunocompromised

Pregnant women

Renal impaired

Estimated number of subjects

1430

Study design details

Setting

This study will be conducted using anonymized Individual Case Safety Reports (ICSRs) submitted to the EudraVigilance Post-Authorization Module (EVPM), covering all European Economic Area countries.

The dataset includes reports related to mRNA COVID-19 vaccines (Pfizer/BioNTech and Moderna), received between 1 January 2020 and 31 December 2023.

All ICSRs with at least one suspected adverse event following immunization (AEFI) will be included, regardless of reporter type, seriousness, or patient demographics.

No exclusion criteria will be applied to ensure the comprehensiveness of real-world data. Subgroup analyses will explore variations in AEFI patterns by age, seriousness, and vaccine version.

Comparators

No formal control group will be used. However, internal comparisons will be made between vaccine brands (Pfizer/BioNTech vs. Moderna) and across different vaccine versions.

Stratified analyses will also compare AEFI profiles by patient age groups and seriousness classification.

These internal comparators will enable indirect assessment of differences in safety profiles across products and population subgroups.

Outcomes

Primary outcomes include the identification and characterization of adverse event clusters following mRNA COVID-19 vaccination, based on co-occurrence patterns of AEFI.

Secondary outcomes involve assessing differences in AEFI profiles between vaccine brands and versions, seriousness classification (serious vs. non-

serious), and specific populations of interest (e.g., older adults, immunocompromised, pregnant women).
Outcomes will be measured using frequency counts, co-occurrence networks, and correspondence analysis.

Data analysis plan

Descriptive statistics will be used to summarize the distribution of ICSRs by year, vaccine version, age group, and seriousness. Co-occurrence analysis will identify frequently co-reported AEFI pairs using hypergeometric testing. Statistically significant associations will be visualized through network plots. Correspondence analysis will explore relationships between vaccine versions and AEFI patterns. Analyses will be performed globally and within relevant subgroups (e.g., age, seriousness).
Statistical analyses will be conducted using R software, following STROBE and ENCePP methodological guidance.

Summary results

We retrieved 993,199 ICSR (Moderna: 394,484; Pfizer: 605,794), with most reports related to women patients (69%) and non-healthcare professionals (65%). A total of 10,804 distinct AEFI terms were described across the retrieved ICSR, with a cumulative occurrence frequency of 3,558,219 (Moderna: 1,555,638; Pfizer: 2,031,828). The most prominent serious clusters included headache, fatigue, pyrexia, myalgia, arthralgia, malaise, nausea, and chills, which frequently co-occurred with vaccination failure. Specific AEFI like fever, chills, malaise, arthralgia, injection site pain, inflammation, and warmth were more often linked to Moderna, while Pfizer was more commonly associated with vaccination failure, menstrual disorders (heavy menstrual bleeding and dysmenorrhea), and hypoesthesia.
In older adults, serious clusters included confusional states, cerebrovascular accidents, and myocardial infarctions, while myocarditis and pericarditis were

noted in younger males. Although rare, serious systemic AEFI, like anaphylactic reactions, were identified but require further causality evaluation.
The overall safety of mRNA COVID-19 vaccines for mass vaccination is supported, but continuous pharmacovigilance remains essential.
Identified clusters of AEFI, particularly serious and systemic ones, although rare and potentially influenced by other underlying causes, underscore the need for continuous monitoring and further epidemiological investigations to explore potential causal relationships.

Documents

Study results

fmed-2-1501921.pdf (7.73 MB)

Study publications

https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2025.150192...

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

This study has been awarded the ENCePP seal

Conflicts of interest of investigators

EUPAS43083-43229.pdf (95.92 KB)

Composition of steering group and observers

EUPAS43083-43230.pdf (155.05 KB)

Data sources

Data source(s), other

EudraVigilance

Data sources (types)

Spontaneous reports of suspected adverse drug reactions

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No