Effectiveness of heterologous and booster Covid-19 vaccination in 5 European countries, using a cohort approach in children and adults with a full primary Covid-19 vaccination regimen (Covid Vaccines Effectiveness (CoVE))

First published: 17/06/2022

Last updated: 07/01/2026

Study Finalised

Administrative details

EU PAS number

EUPAS47725

Study ID

50294

DARWIN EU® study

No

Study countries

- [ ] France
- [ ] Italy
- [ ] Netherlands
- [ ] Spain
- [ ] United Kingdom

Study description

Real-world effectiveness data demonstrated that Covid-19 vaccines' protection against severe SARS-CoV-2 infection is high in the short term but wanes over time, also depending on the virus variants. This study will deepen the real-world data effectiveness evidence of heterologous, homologous, and booster vaccination different regimes on a large population scale. The goal of this study is to assess the effectiveness and waning of immunity of primary Covid-19 vaccinations and the booster in preventing different covid-19 outcomes. The Primary objective is to estimate the effectiveness and waning of effectiveness in adults and adolescents (heterologous vs homologous primary vaccinations), children (vaccinations vs non-vaccination), homologous or heterologous booster vs no booster. Secondary objective: To estimate the effectiveness of booster against all-cause mortality in adults 60+. Retrospective multi-database cohort study. Cohort entry (time0) is the date of the 2nd dose for the primary vaccination regimens, or the booster. The same date for pairs who are matched on time0, birth year, sex and region. Outcomes: severe Covid-19, Covid-19-related death, all Covid-19 infections, and all-cause mortality. The study will include 8 data sources across from Spain, Italy, Netherlands, France, and United Kingdom. The population are estimated in around 67 millions patients with complete primary vaccination. Baseline characteristics, Incident rates differences and IPW Kaplan-Meier curves for covid outcomes by matched cohorts will be estimated. Vaccine effectiveness will be estimated as 1 minus the Hazard Ratio (estimated by Cox regression) for age groups, overall matched cohorts, and brands. Meta-analyses will be performed for small subpopulations.

Different access to Covid-19 testing (restricting to patients with negative tests) and healthy vaccinee effect will be investigated in sensitivity analyses.

Study status

Finalised

Research institutions and networks

Institutions

Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Medical Devices, AEMPS)

Spain

First published: 01/02/2024

Last updated: 04/09/2024

Institution | EU Institution/Body/Agency | Not-for-profit | Regulatory Authority | ENCePP partner

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 23/05/2024

Institution | Educational Institution | ENCePP partner

Servicio de Epidemiología, Prevención y Promoción de la Salud, Instituto de Salud Pública de Navarra (ISPN)

Spain

First published: 03/05/2012

Last updated: 20/08/2024

Institution | Other

EpiChron Research Group on Chronic Diseases, Aragon Health Sciences Institute (IACS)

Spain

First published: 17/02/2017

Last updated: 02/04/2024

Institution | Educational Institution | ENCePP partner

Innovative Solutions for Medical Prediction And Big Data Integration In Real World Setting Srl (INSPIRE Srl), University Of Messina

Italy

First published: 15/11/2021

Last updated: 15/11/2021

Institution | Educational Institution | ENCePP partner

Drug Safety Research Unit (DSRU)

United Kingdom

First published: 10/11/2021

Last updated: 09/01/2026

Institution | Not-for-profit | ENCePP partner

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

RTI Health Solutions (RTI-HS)

France

- [ ] Spain
- [ ] Sweden
- [ ] United Kingdom
- [ ] United Kingdom (Northern Ireland)
- [ ] United States

First published: 21/04/2010

Last updated: 13/03/2025

Institution | Not-for-profit | ENCePP partner

Teamit Institute

- [ ] Spain

First published: 12/03/2024

Last updated: 12/03/2024

Institution | Other | ENCePP partner

l’Assistance Publique-Hôpitaux de Paris (APHP) France, Teamit Institute, S.L. Spain, PHARMO Institute for Drug Outcomes Research. Netherland, Società Servizi Telematici -Pedianet. Italy, Institute of Public Health, Riga Stradins University Latvia, Democritus University of Thrace Greece, National

Public Health Agency (RIVM) Netherlands

Networks

Vaccine monitoring Collaboration for Europe (VAC4EU)

- [ ] Belgium
- [ ] Denmark
- [ ] Finland
- [ ] France
- [ ] Germany
- [ ] Italy
- [ ] Netherlands
- [ ] Norway
- [ ] Spain
- [ ] United Kingdom

First published: 22/09/2020

Last updated: 22/09/2020

Network | Outdated | ENCePP partner

EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network

- [ ] Netherlands

First published: 01/02/2024

Last updated: 24/09/2025

Network

Contact details

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 20/04/2022

Actual: 20/04/2022

Study start date

Planned: 20/06/2022

Actual: 20/06/2022

Date of final study report

Planned: 20/01/2023

Actual: 23/04/2023

Sources of funding

- EMA

Study protocol

D2_StudyProtocol_v0.4_ROC12_FINAL_20220615.pdf (1.12 MB)

Regulatory

Was the study required by a regulatory body?

No

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

Not applicable

Other study registration identification numbers and links

The project has received support from the European Medicines Agency under the Framework service contract nr EMA/2020/46/TDA/L5.06

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

a retrospective cohort study

Main study objective:

The goal of this study is to assess the effectiveness and waning of immunity of primary Covid-19 vaccinations and the booster in preventing different covid-19 outcomes.

Study Design

Non-interventional study design

Cohort

Other

Non-interventional study design, other

Retrospective multi-database study

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(J07BN) Covid-19 vaccines

Covid-19 vaccines

Medical condition to be studied

SARS-CoV-2 test positive

Additional medical condition(s)

Severe Covid-19 (i.e. admitted to hospital or intensive care units) Covid-19-related death, all Covid-19 infections, all-cause mortality (secondary objective)

Population studied

Short description of the study population

The study population comprised of all children, adolescents, and adults, had at least 2 years of available healthcare data registered in the 6 electronic health care databases for the study period of December 2020 to February 2022.
The study also included vaccinated individuals with at least two recorded vaccinations since the start of the study period.

Age groups

- Children (2 to < 12 years)
- Adolescents (12 to < 18 years)
- 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

Other

Special population of interest, other

COVID-19 patients

Estimated number of subjects

67271319

Study design details

Setting

We retrospectively used data from 6 electronic health care databases in Southern, Northern, and
Western Europe: the Italian Caserta local health database (IT-INSPIRE srl), the Italian Societa Servizi Informatici (IT-PEDIANET) database, the Spanish Pharmacoepidemiological Research Database for Public Health System (ES-BIFAP), the Spanish Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (ES-SIDIAP) database, the Dutch PHARMO Database Network (NL-PHARMO), and the British Clinical Practice Research Datalink (UK-CPRD) Aurum.

Outcomes

covid-19 (positive test and/or diagnosis) severe covid-19 covid-19 related death, all-cause mortality

Data analysis plan

Distributions of baseline and Covid-19 vaccination characteristics at time0 will be assessed in all-Covid-19 vaccinated population and matched populations. Incident rates differences (95% confidence intervals) of each Covid-19 outcome

for both primary vaccination matched and booster/non-booster matched cohorts estimated by overall, age groups, brands, and time since (booster-)time0 will be estimated. IPW-weight Kaplan-Meier curves will be generated to depict the cumulative incidence of the outcomes by matched cohorts over time after (booster-)time0. Cox proportional hazards regression (95% confidence intervals) to derive the average hazard ratio (HR) of Covid-19 related outcomes will be produced. The adjusted vaccine effectiveness for all the outcomes and all-cause death will be estimated as 1 minus the adjusted HR (and 1-95% confidence intervals) for age groups, overall matched cohorts, and brands.Random-effects meta-analyses will be performed in subpopulations reduced in number.

Documents

Study, other information

ROC12_CoVE_Abstract.pdf (816.91 KB)

Study publications

Castillo-Cano B, Riefolo F, Villalobos F, Martín-Pérez M, Messina D, Elbers R, ...

Riefolo F, Castillo-Cano B, Martín-Pérez M, Messina D, Elbers R, Brink-Kwakkel ...

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.

Data sources

Data source(s)

BIFAP - Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (Pharmacoepidemiological Research Database for Public Health Systems)

Pedianet

ARS Toscana

PHARMO Data Network

The Information System for Research in Primary Care (SIDIAP)

Caserta claims database

Clinical Practice Research Datalink

Data source(s), other

SNDS (Système National des Données de Santé) France

Data sources (types)

Administrative healthcare records (e.g., claims)

Disease registry

Drug registry

Electronic healthcare records (EHR)

Other

Data sources (types), other

Secondary care electronic patients registry, Hospital registry

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