Real-World Effectiveness of COVID-19 Vaccines in the Netherlands: Causal Inference From A Retrospective Cohort Study Using the Target Trial Emulation framework Within the PharmLines Initiative

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000000785

Study ID

1000000785

DARWIN EU® study

No

Study countries

Netherlands

Study description

We will conduct a retrospective population-based new-user cohort study using linked individual-level
data from the Lifelines cohort, Statistics Netherlands (CBS), and the IADB.nl pharmacy database. Daily target
trials will be sequentially emulated between June 18, 2021 and October 19, 2022. Adults without prior SARS
CoV-2 infection will be assigned to partially vaccinated, fully vaccinated, booster-vaccinated, or unvaccinated
strategies according to their eligibility at each trial start. The primary outcome is time to first laboratory-confirmed
SARS-CoV-2 infection determined by RT-PCR testing. Generalized additive models will estimate time-varying
hazard ratios, while pooled logistic regression will estimate odds ratios for predefined post-vaccination intervals.
Inverse probability of treatment and censoring weights, multiple imputation, and prespecified sensitivity analyses
will address confounding, informative censoring, and missing data.

Study status

Ongoing

Research institutions and networks

Institutions

University of Groningen

Netherlands

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Institution | Educational Institution

Contact details

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 01/05/2025

Actual: 01/05/2025

Study start date

Planned: 01/11/2025

Actual: 01/11/2025

Data analysis start date
Planned: 01/12/2025

Actual: 01/10/2026

Date of final study report
Planned: 01/04/2027

Sources of funding

- No external funding

Study protocol

HARPER_protocol_TTE_VaccineEffectiveness_Lifelines-CBS-v4.pdf (722.3 KB)

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:

Effectiveness study (incl. comparative)

Method development or testing

Data collection methods:

Secondary use of data

Study design:

Retrospective cohort study

Main study objective:

Comparing the estimates of this retrospective cohort study using a sequential Target Trial Emulation approach with the estimates of a Test-Negative Case-Control study (yet to be published)

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

COMIRNATY

VAXZEVRIA

COVID-19 VACCINE (INACTIVATED, ADJUVANTED)

Medical condition to be studied

COVID-19

SARS-CoV-2 test positive

Population studied

Short description of the study population

Dutch citizens of Northern regions of the Netherlands

Age groups

- **In utero**
- **Paediatric Population (< 18 years)**
  - Neonate
    - Preterm newborn infants (0 – 27 days)
    - Term newborn infants (0 – 27 days)
  - Infants and toddlers (28 days – 23 months)
  - Children (2 to < 12 years)
  - Adolescents (12 to < 18 years)
- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)

- Adults (85 years and over)

Study design details

Setting

Population-based, respondents to the Lifelines questionnaires, registered in IADB.nl (Pharmlines initiative).

Comparators

Unvaccinated participants

Outcomes

SARS-CoV-2 infection; severe COVID-19 disease; hospitalization; ICU-admission; all-cause mortality

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Data analysis plan

We apply Inverse Probability of Censor (IPC) weights to adjust for the introduced informative censoring of getting vaccinated after time0 aka those who deviate from the assigned treatment strategy – by weighting the data. IPC upweights those that remain uncensored to get a population that better represent what would have happened without informative censoring.
We apply Inverse Probability of Treatment (IPT) weights to balance the four exposure groups on their observed covariates at baseline.
For studying the time-variation of vaccine protection generalized additive models (GAMs) with smoothing splines will be fitted to the data using the mgcv package in R. The parametric part of the model included linear effects from potential confounders while time elapsed since the index date will be modelled non-parametrically using penalized thin plate regression splines.
As we would like to compare the results of the retrospective cohort study to the results of the test-negative case control study, which used a conditional logistic

regression model yielding odds ratios across post-vaccination time-intervals (14-28 days since vaccination, 29-82 days, 83-181 days, 181-364 days and 365+ days), our primary analysis will make use of a pooled logistic regression model using the same discrete time intervals, since these yield odds ratios. These can then be converted to vaccine effectiveness percentages.
To account for missing covariate data, the models described above will be fitted separately in each of the multiply imputed datasets.
For the GAM, pooling spline coefficients for penalized smooths can be affected by the smoothing parameter estimation. To avoid this, we will generate model-based predictions and corresponding standard errors for each imputed dataset. At each time elapsed since the index date, the predicted linear-predictor contrasts and their within-imputation variances will be combined across imputations using Rubin's rules. The pooled effects are then exponentiated.

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)

Lifelines Data and Biobank

IADB.nl

Data source(s), other

Dutch vaccination records (Statistics Netherlands)

Data sources (types)

Patient surveys

Pharmacy dispensing records

Vaccination 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