Real-world effectiveness of SARS-CoV-2 primary vaccination against SARS-CoV-2 infection: observational federated study across several EU regions

Key words

Vaccine effectiveness; COVID-19; Secondary use of data; Federated research infrastructure

Date

13 April 2023

Version

Version	Description
1.0.0	First draft of the baseline use case protocol (WP5 T5.2)
1.0.1	Corrected the duration of BY-COVID research project until 30 September 2024
1.0.2	Adapted the introduction (added reference to the VIEW-hub resource, added more information on causal inference), changed details in Table 1 (e.g., definition of previous infection, secondary analysis), adapted Figure 2. Some of these adjustments may result in an updated common data model.
1.0.3	Adapted enrollment period (January 1, 2021 until September 1, 2021)

Research team

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Study rationale

Background

In the beginning of 2021, large-scale severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination campaigns were initiated in European countries, resulting in a high coverage of primary vaccination, e.g., 83% and 92% of respectively the population of Belgium and Aragon (Spain) older than 5 years (i.e., eligible to be vaccinated) had received at least a complete primary vaccination schedule by the end of 2022 (1,2).
To assess the effectiveness of primary vaccination in preventing different outcomes (i.e., evaluating an intervention effect), randomised controlled trials (RCTs) are considered the “gold standard”. However, often we need to resort to observational analyses of existing real-world data when the randomised trial that would answer our causal question - the “Target Trial” - is not feasible, ethical and timely (3). In addition, RCTs have notable limitations of sample size and subgroup analysis, restrictive inclusion criteria, and a highly controlled setting that may not be replicated in a mass vaccine rollout (4). Indeed, RCTs may not reflect the real-world effectiveness (RWE) of the vaccines (5).

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Previous real-world observational studies in Europe suggest that the completion of a primary vaccination schedule protects against (symptomatic) infection (4,6–8). The International Vaccine Access Center (IVAC; Johns Hopkins Bloomberg School of Public Health, US) maintains the online VIEW-hub resource (9) which contains real-world epidemiological data on vaccine type and usage, country coverage, and vaccine impact. A living systematic review and meta-analysis is carried out (*weekly updated*) on the "*Post-Authorisation COVID-19 Primary Series Vaccine Effectiveness*". However, the real-world studies included in this review encompass a wide range of methodologies, populations, and outcome measures. Indeed, these single-country observational studies are often conducted within (sub)populations with specific characteristics, taking into account different confounding factors and using different statistical methodologies. As such, generalisability and comparability of these results across federations is limited.
Although there is no perfect method for estimating a causal effect in observational data (10), conceptual frameworks exist to guide the design and analysis of observational studies in order to limit apparent paradoxes and common biases and increase the transportability of estimates (3,11). In fact, causal inference from observational databases can be viewed as an attempt to emulate a randomised experiment (the "Target Trial") to answer the question of interest (3). In this study, the effectiveness of SARS-CoV-2 primary vaccination in preventing SARS-CoV-2 infection is assessed across national borders, using a framework for causal inference. The well-defined causal analysis methodology will subsequently be deployed across federations to reproduce the analysis and pool the aggregated results. We aim to inform high-level vaccine policy by leveraging real-world observational data from multiple data sources hosted in multiple sites (i.e., countries).

Research question/objectives

We aim to investigate the real-world effectiveness of SARS-CoV-2 primary vaccination as compared to partial or no vaccination in preventing SARS-CoV-2 infection in virtually all resident populations spanning different countries. The study will be conducted in two sequential stages, expanding the exercise to several countries/regions:

- Stage I (pilot): Aragon (Spain) and Belgium.
- Stage II: Aragon (Spain), Belgium, Austria, Finland, Norway, Estonia and The Netherlands. The participation of these countries/regions is conditional on data access.

Methodology

Study design and context

The study design is an observational retrospective longitudinal (cohort) study using routinely collected administrative, social, health and care data from several

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countries/regions in Europe. We have designed the observational study to emulate a hypothetical Target Trial (TT) of *the causal effect of SARS-CoV-2 vaccination programmes in preventing SARS-CoV-2 infections*.

Target Trial specification and emulation

The key components of the target trial and its subsequent emulation are explicitly described in Table 1. Several of the key components are part of the widespread population, intervention, control, and outcome (PICO) approach to the formulation of clinical questions (12).

Table 1. Protocol of the target randomised control trial and target trial emulation by using observational data.

Protocol Component	**Target Trial Specification (*Ideal Hypothetical Trial*)**	**Target Trial Emulation (*Actual Study Design reusing Real World Data*)**
Eligibility criteria	• **Study population:** All individuals eligible to be vaccinated. • **Enrollment period**: From the start of the SARS-CoV-2 vaccination campaign (January 1, 2021) to the start of the SARS-CoV-2 booster vaccination campaign (September 1, 2021). • **Age**: 5 to 115 years old, included (*all individuals eligible to be vaccinated*). • **Previous infection**: Individuals without a SARS-CoV-2 infection before enrolment. • **Country**: Individuals living in the respective country	• **Study population**: All individuals vaccinated with at least one dose of the SARS-CoV-2 vaccine (any of the available brands) and all individuals eligible to be vaccinated with a documented positive diagnosis (irrespective of the type of test) for SARS-CoV-2 infection during the data extraction period. • **Enrollment period**: From the start of the SARS-CoV-2 vaccination campaign (January 1, 2021) until the start of the SARS-CoV-2 booster vaccination campaign (September 1, 2021). • **Age**: 5 to 115 years old, included (*all individuals eligible to be vaccinated*). • **Previous infection**: Individuals without a documented confirmed infection before completing the primary vaccination schedule (i.e. enrolment) or before January 1, 2021 (SARS-CoV-2 vaccine roll-out) for those not having completed a primary vaccination schedule (controls). • **Country**: Resident of the respective country We apply these eligibility criteria to the data obtained by performing a full join of the registered individuals in the COVID-19 cases and vaccination datasets. Individuals with neither a registered vaccine dose nor a positive diagnosis during the data extraction period are therefore excluded.
Treatment strategies	<u>Primary analysis</u> 1) Completing a primary vaccination schedule (from any vaccine brand) 2) Not completing a primary vaccination schedule (either not receiving a vaccine or being only partially vaccinated). <u>Secondary analysis</u> 1) Completing a homogeneous primary vaccination schedule with	Same as in Target Trial Specification. Vaccination status ascertainment (including brand, dose and date) based on the vaccination registry. Date of being primary vaccinated (completing a primary vaccination schedule) is considered as 14 days after receiving the final dose of the primary vaccination schedule (*one dose for the Johnson-Johnson vaccine and two doses of any of the other vaccines considered*).

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	a specific brand (BioNTech-Pfizer, Moderna, Johnson-Johnson, Astrazeneca, Novavax) 2) Not completing a primary vaccination schedule (either not receiving a vaccine or being only partially vaccinated). Pragmatic trial: strategies compared under the usual conditions.	
Assignment procedures	Participants will be randomly assigned, at baseline, to either completing the primary vaccination schedule or to not completing the primary vaccination schedule (no or only partial vaccination). The participants will be aware of the strategy to which they have been assigned (i.e., without blind assignment).	To mimic randomization, we need to adjust for all confounding factors required to ensure comparability (conditional exchangeability) of the groups defined by vaccination (*as identified in the Directed Acyclic Graph* (13)). We assume that individuals are randomly assigned within levels of baseline covariates: Age, Gender, Comorbidities, ImmuneStatus, EssentialWorker, Foreign, Institutionalised people, Pregnancy, and ResidenceArea. The adjustment will be performed via matching.
Follow-up period	• Starts, for each individual, at randomization to one of the vaccination strategies (baseline) • Ends at diagnosis of SARS-CoV-2 infection (i.e., outcome of interest), death, loss to follow-up, the date of receiving a booster dose, 168 days after baseline (24 weeks), or the end of the study period (March 1, 2022), whichever occurs first.	Sequential trial emulation: • Starts, for each individual: ○ Vaccine group: time of completing a primary vaccination schedule ○ No (or partial) vaccine group: first eligible time (time of completing a primary vaccination schedule of the matched pair) • Ends at diagnosis of SARS-CoV-2 infection, death (all causes), vaccination (for unvaccinated controls), completed primary vaccination of the matched control (for vaccinated persons), booster dose (for vaccinated persons), booster dose of the matched vaccinated person (for unvaccinated controls), or the end of the study period (i.e., the most recent date at which data is available at time of analysis). Loss to follow-up due to emigration or 'disenrollment' from the health care system not taken into account. Newly vaccinated individuals (completing a primary vaccination schedule) are eligible for inclusion in the "vaccine group" of the study, even if they had previously been selected in the "no vaccine group" (as controls).
Outcome	Laboratory-confirmed SARS-CoV-2 infection	A documented laboratory-confirmed SARS-CoV-2 infection, thus excluding self-reported test results
Causal contrast of interest	Per-protocol effect.	Observational analog of the per-protocol effect.

In the target trial (Figure 1), eligible participants are enrolled from January 1, 2021 (start of the SARS-CoV-2 vaccination campaign) until September 1, 2021 (start of the SARS-CoV-2 booster vaccination campaign). As such, the enrolment period in the target trial covers a

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period of 9 months. For each eligible participant, follow-up starts at the moment of randomisation (baseline, t_0) and ends at diagnosis of SARS-CoV-2 infection (outcome of interest), death, loss to follow-up, receiving a booster dose, or 6 months after baseline. The period of data collection runs until March 1, 2022 to allow for a minimal follow-up period of 6 months for those participants with baseline (t_0) at the end of the enrollment period.

In the sequential emulated target trial (Figure 2), each eligible individual is considered as a different individual at each eligible time (i.e., *daily*). As such, a sequence of nested (*daily*) trials are emulated with increasing time (t_1, t_2, ..., t_n), iterating over the days in the enrollment period. At each eligible time during the enrollment period, the vaccination status of eligible individuals is assessed and every individual who has completed a primary vaccination schedule at that time (*treated/exposed*) is matched to an individual who has not (yet) completed the primary vaccination schedule (*control*). Newly vaccinated individuals (completing a primary vaccination schedule) are eligible for inclusion in the study, even if they had previously been selected in the "no (or partial) vaccine group". Follow-up ends at diagnosis of SARS-CoV-2 infection, death, death of matched person, completed primary vaccination (for unvaccinated or partially vaccinated controls), completed primary vaccination of the matched control (for primary vaccinated persons), booster dose (for primary vaccinated persons), booster dose of the matched vaccinated person (for unvaccinated or partially vaccinated controls), or the end of the study period. The study period ends at the most recent date at which data is available at the time of analysis. The data extraction period starts from the date of the first documented SARS-CoV-2 infection, in order to appropriately identify individuals with a previously documented SARS-CoV-2 infection.

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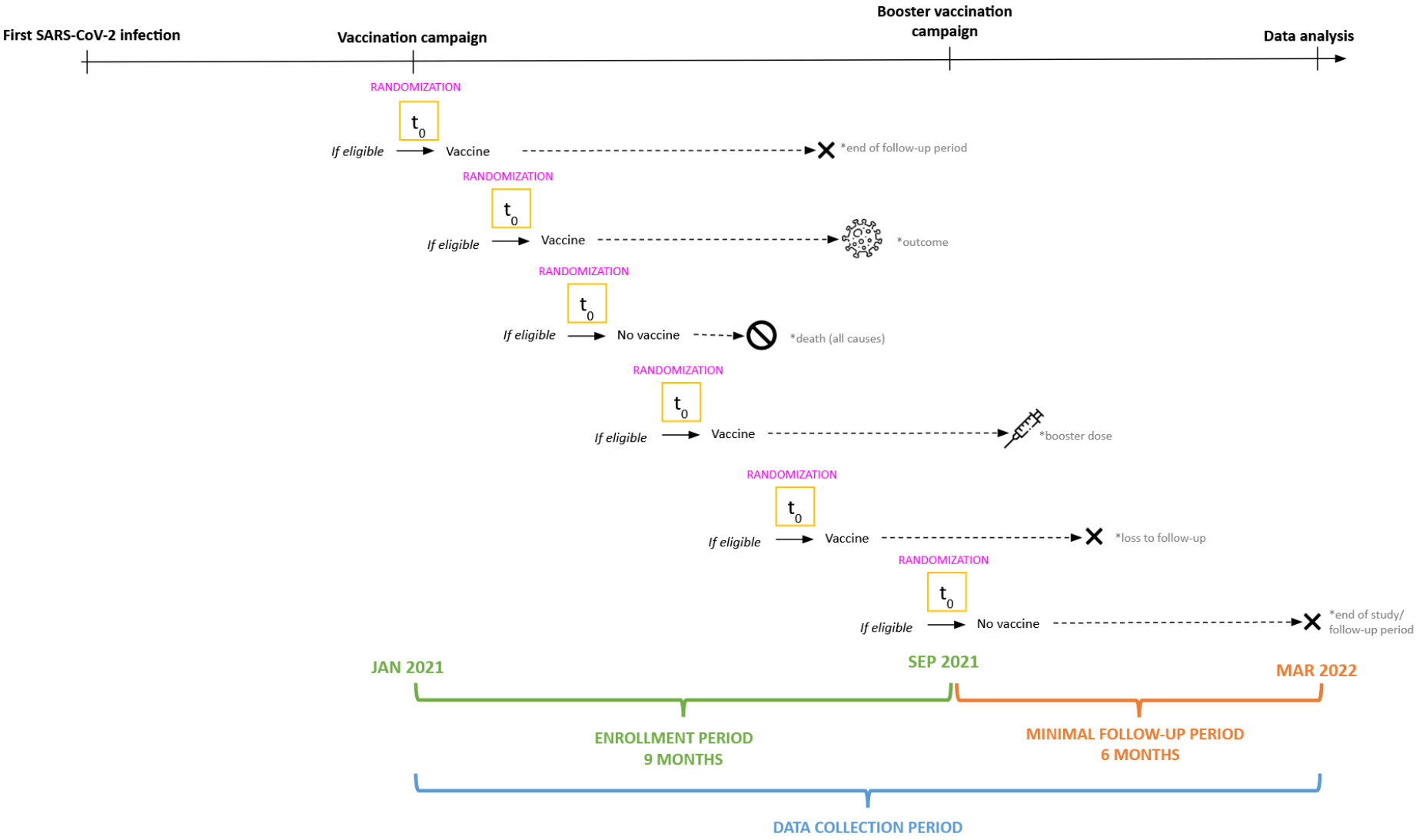

Figure 1. Timeline of the target trial (ideal hypothetical trial).

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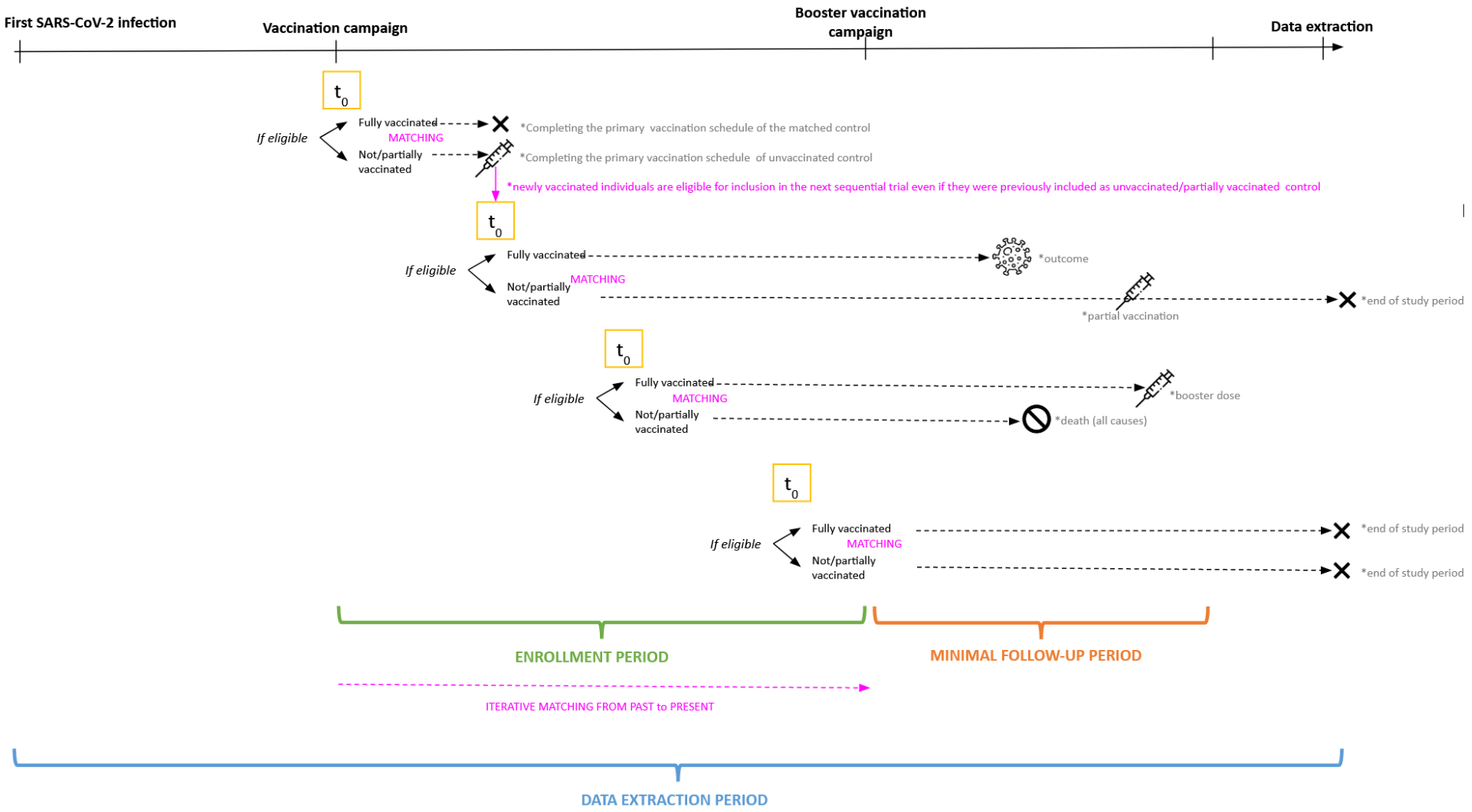

Figure 2. Timeline of the sequential emulated target trial (actual study design reusing Real World Data).

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Sources of information

The analysis requires the secondary use of individual level data from COVID-19 registries (*COVID-19 public health surveillance and monitoring information system of COVID-19 cases and SARS-CoV-2 vaccination population registry*), insurance registry or health system users databases (*i.e., patient administrative information*) or data from Electronic Health Records (EHR, *i.e., comorbidities*), and death registration data. All data sources contain routinely collected data both from healthcare or public health information systems. For the variables required for the study, we refer to the common data model specification published in Zenodo (14).

A full join of the COVID-19 cases and SARS-CoV-2 vaccination records, linking all registries using unique pseudonyms at individual level, will be performed to obtain all people vaccinated with at least one dose of the SARS-CoV-2 vaccine (any of the available brands) in a resident area and/or with a documented positive diagnosis (irrespective of the type of test) for SARS-CoV-2 infection (COVID-19). In addition, linkage of patient administrative information and information on patient comorbidities is required to account for confounding factors (age, gender, comorbidities, immune status, foreign, pregnancy, residence area, essential worker, institutionalised) in the causal inference analysis. Data extraction is foreseen from the first date of a documented SARS-CoV-2 infection in the population until the most recent date at which data is available at the time of analysis. Park et al. (15) adopted a comparable approach to obtain data from the Korean COVID-19 vaccine effectiveness cohort, in their study comparing the effectiveness of two vaccines in preventing SARS-CoV-2 infection. They linked a registry with all COVID-19 laboratory-confirmed cases and a registry with SARS-CoV-2 vaccination data in South Korea.

Each country/region (Aragon (Spain), Belgium, Austria, Finland; Norway, Estonia and The Netherlands) will pull the data from their respective data sources conditional on data availability and access.

Participants

The analysis will be based on the secondary use of routinely collected data, individuals are not recruited. The study population consists of all residents of a country/region vaccinated with at least one dose of any SARS-CoV-2 vaccine and those eligible to be vaccinated with a documented positive diagnosis for SARS-CoV-2 infection (irrespective of the type of test) during the data extraction period. People who are not a resident of the participant country or region and people who have had a documented confirmed SARS-CoV-2 infection before completing the primary vaccination schedule (i.e. enrolment) or before January 1, 2021 (SARS-CoV-2 vaccine roll-out) for those not having completed a primary vaccination

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schedule (i.e. matched controls), are excluded from the analysis. Sample sizes will depend on the data available in the data sources.

Statistical analysis plan

An initial exploratory and data quality analysis will be performed, checking pre-specified validation rules and missingness. Imputation will be performed in variables considered as core variables for the analysis.

Randomization is mimicked by matching on all confounding factors required to ensure comparability (conditional exchangeability) of the groups defined by vaccination (as identified in the Directed Acyclic Graph, see causal model specification published in Zenodo (13)). For each day during the enrollment period (i.e., sequential emulated trial), all newly vaccinated individuals (i.e. those having completed the primary vaccination schedule) will be matched in a 1:1 ratio to unvaccinated (or partially vaccinated) controls based on the variables listed in the adjustment set to close non-causal backdoor paths and so, eliminate confounding bias (16): age, gender, residence area, pregnancy, being an essential worker, being institutionalised, being a foreigner, presence of comorbidities, and the immune status. Presence of comorbidities is defined as having one of the following conditions: diabetes, obesity, health failure, COPD, a solid tumour without metastasis, chronic kidney disease, sickle cell disease, chronic liver disease, and hypertension (*see the data model specification published in Zenodo* (13) *for variable-level specification, including data dictionaries and crosswalks defining each variable using several international disease classification systems*). Immune status is defined as having one of the following conditions: blood cancer, transplantation, HIV infection, primary immunodeficiency, immunosuppression (*see the data model specification published in Zenodo* (13) *for variable-level specification and crosswalks*).

The matching will be performed using exact matching (*whenever possible*) or distance based algorithms such as nearest neighbour matching based on the Mahalanobis distance based on the probability of intervention (vaccination) for those individuals not matched using exact matching. Covariate balance after matching will be evaluated considering mean differences between variable values (standardised for continuous variables) between vaccinated and unvaccinated groups, with a difference of 0.1 or less considered to be acceptable.

For each person, follow-up ends at the occurrence of the outcome event (i.e., a confirmed SARS-CoV-2 infection), death (all causes), completing primary vaccination (for unvaccinated or partially vaccinated controls), completing primary vaccination of the matched control (for vaccinated persons), vaccination with a booster dose (for vaccinated persons), vaccination with a booster dose of the matched vaccinated person (for unvaccinated or partially vaccinated controls), or the end of the study period (i.e., the most

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recent date at which data is available at time of analysis). Newly vaccinated persons (completing a primary vaccination schedule) are eligible for inclusion in the study, even if they have previously been selected as a control. As such, the matched controls enrolled at a particular day during the enrollment period are those who are unvaccinated (or partially vaccinated) at this date but may receive a first (or second) vaccination dose at a later date during the data extraction period.

Differences in the occurrence of a SARS-CoV-2 infection (as a time-to-event outcome) between primary vaccinated and unvaccinated or partially vaccinated individuals (average treatment effect, ATE (16)) will be computed by using adjusted Cox proportional-hazards models (17), and hazard ratios (HRs) and a robust variance estimate will be obtained.

A secondary analysis will be performed where the effectiveness of primary vaccination in preventing SARS-CoV-2 infection is assessed for different vaccine brands (e.g. BioNTech-Pfizer, Moderna, Johnson-Johnson, Astrazeneca, Novavax), hence conducting a stratified analysis using the matched pairs constructed for the primary analysis. Further, we can assess vaccine effectiveness during different time periods, with a dominant circulation of different SARS-CoV-2 variants.

Several sensitivity analyses will be performed accounting for different imputation algorithms, and different matching algorithms and compared in covariate balance after matching, robustness of the survival estimate and computing efficiency of the algorithm.

HRs and variance estimates will be collected from each country or region, and a meta-analysis will be performed in which the HRs are pooled by using the inverse variance method (18).

Ethical aspects

Balance risk/benefit

It is a population-wide retrospective observational longitudinal study, based on the secondary use of routinely collected social, health and care data from healthcare systems. As such, the intervention already took place preceding the study and there is no risk associated with participating in the study. Potential benefits derived from the study would be applied to the design and development of future vaccination programs at population level.

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Treatment of personal data

Pseudonymized individual level data will be managed and analysed within the premises of contributing partners (data hubs, i.e. any institution holding or having access to the data), according to a predefined data model (14) specific to the research question (minimisation principle). Data is securely stored within the premises of the participant data hub. Access to this environment will only be provided to researchers involved in the completion of the project. All people authorised to manage the data will be subject to a non-disclosure agreement (NDA). Pseudonymized individual level data will only be processed for uses within the scope of the purposes of the present study and will not be shared with any third party. An analytical pipeline, developed by the project coordination hub, will be implemented within the secured processing environment using the transformed data as input. Extraction of aggregated results from the secured processing environment might be required to complete the purposes of the project involving comparative analysis between countries/regions. All country/region disclosure policies will be respected when producing and sharing aggregated outputs for comparison or publication. Finally, the scripts of the analytical pipeline and outputs will be published as open source using Zenodo using a CC-BY 4.0 International licence following the FAIR principles. In addition, the workflow can be also documented and published as an RO-Crate using WorkflowHub, in coordination with BY-COVID WP4. A Data Management Plan (DMP) is produced using ARGOS (OpenAIRE) and is subsequently published in Zenodo (19). The DMP will continuously be updated as new nodes join the baseline use case.

Healthcare implications

There are no implications for healthcare processes. Results of this study could potentially influence future decisions on public health interventions (i.e., future vaccination campaigns).

Informed consent

Informed consent is waived based on art. 6 and 9 of the GDPR. The collection is allowed based on general interest (art. 6 GDPR) and regarding article 9 § 2 of the GDPR: processing is necessary for reasons of public interest in the area of public health, such as protecting against serious cross-border threats to health, or ensuring high standards of quality and safety of health care and of medicinal products or medical devices, on the basis of Union or Member State law which provides for suitable and specific measures to safeguard the rights and freedoms of the data subject, in particular, professional secrecy.

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Use of biological samples

No biological sample tissues, embryos or totipotential cells will be used. No genetic analyses will be performed.

Compensation to study participants

No compensation is provided to study participants.

Insurance policy

No insurance policy is required.

Conflict of interest

The researchers declare no conflict of interest.

Chronogram

Duration of this research project is until 30 September 2024.

Funding

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Timeline: 1 October 2021 - 30 September 2024

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Annex I - Supporting documentation

A causal model (DAG), a common data model specification and a simulated dataset following the specifications of the common data model are available at https://doi.org/10.5281/zenodo.6913046

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